

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207999Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

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| Date | 5/25/2016 |
| From | Lara Dimick-Santos, MD |
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| Proprietary Name / Non-Proprietary Name | OCALIVA/Obeticholic Acid |
| Dosage form(s) / Strength(s) | 5 mg and 10 mg tablets |
| Applicant Proposed Indication(s)/Population(s) | (b) (4) |
| Recommendation on Regulatory Action | Approval |
| Recommended Indication(s)/Population(s) | For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. |

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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Primary biliary cirrhosis, recently renamed primary biliary cholangitis (PBC) is a rare, serious and life-threatening disease that predominantly affects women (women:men - 10:1). PBC is a chronic, slowly progressive autoimmune, cholestatic liver disease characterized by inflammatory destruction of interlobular and septal bile ducts. The disease is heterogeneous in presentation, both in symptoms and time to progression of disease. The typical age of onset is 40-60 years. The incidence of PBC in the U.S. is 4.5 per 100,000 women and 0.7 per 100,000 men (PBC is known to be more common in women). The prevalence was estimated at 65.4 for women and 12.1 for men per 100,000. PBC affects approximately 1/1000 women over the age of 40. Other conditions such as osteopenia/porosis, hyperlipidemia, and fat soluble vitamin deficiency and other autoimmune diseases are common. Fatigue and pruritus are the two most common symptoms in PBC patients earlier in the disease course and can be disabling. The disease is more aggressive and less responsive to treatment with ursodeoxycholic acid (UDCA, the only approved therapy), in patients <30 years of age at diagnosis, in men and in patients with symptoms of fatigue and pruritus.

There is one approved treatment for PBC, ursodeoxycholic acid (UDCA) which was approved in 1997. Approximately 50-60% of patients have an adequate biochemical response to UDCA and it appears that patients who are responsive have a nearly normal life expectancy (the 5, 10 and 15 year survival is 90%, 78%, and 66% respectively). However, about 40% of patients have an inadequate response to UDCA and studies have shown these patients have a poor prognosis with progress to liver failure. A small percentage of patients (< 5%) are intolerant to UDCA secondary to gastrointestinal adverse reactions and hair loss. With liver transplantation PBC recurrences are noted. Therefore, there is an unmet medical need for effective treatment for patients with PBC who are intolerant to or who have an inadequate response to UDCA. (Section 2)

Obeticholic acid (OCA) is a new molecular entity that is a modified bile acid. OCA is a potent farnesoid X receptor (FXR) agonist. FXR activation inhibits bile acid synthesis and promotes bile flow (choleresis). (b) (4) Like other bile acids OCA is conjugated to glyco-OCA and tauro-OCA and like other bile acids, OCA and its conjugates undergo extensive enterohepatic recirculation and therefore have a long half-life.

The review of this application hinged on the acceptance of the change in biomarkers (surrogate endpoint) to be reasonably likely or not to predict clinical benefit. To support use of a biomarker endpoint the Applicant supported the efforts of an academic group to gather better data on PBC patients. The Global PBC Study Group was formed and published results by conducting retrospective analyses on 4,845 PBC patients from multiple sites in Europe and the US, and found ALP and total bilirubin (TB) levels as a composite endpoint, at one year of treatment with UDCA, prognosticates death and liver transplantation. The Division agreed with allowing submission of an application using a composite surrogate endpoint under the accelerated approval program. However, when the application was submitted it became apparent that the majority (92%) of

patients enrolled in the phase 3 trial had early stage PBC and thus had normal TB at enrollment. Therefore, the change in ALP was the driver of the endpoint results. The Division via the Applicant approached The Global PBC Study Group to obtain access to the data sets to allow analysis of a subset of patients that matched patients in the phase 3 trial to ascertain if ALP reduction alone was predictive of clinical benefit (death and transplant) in patients taking UDCA. After some delay in obtaining the data, requiring a major amendment for the application, the data was submitted as a DMF file to the FDA. The Applicant did not have access to this data, but was allowed access to the results of the analysis. The results of the analysis of the Global PBC Study Group data by an independent statistician at the FDA did show that change in ALP alone at one year was predictive of clinical benefit in patients with early stage PBC taking UDCA. The statistical reviewer analyzed multiple cut-points for ALP and found a best-fit stratified endpoint (See Section 7.2). This best-fit endpoint was also used for an exploratory analysis of the phase 3 trial data and supported that there was statistically significant change in ALP in the treatment arms as compared to placebo (see Section 7.7). The variability in ALP in the population was assessed as well as the variability of the assay. The team agreed that the data supported that ALP reduction was predictive of clinical benefit for patients taking UDCA, and that taking all the data into consideration, it was reasonably likely that ALP reduction to below $1.67 \times \text{ULN}$ and by at least 15% would be predictive of clinical benefit for patients taking OCA.

The efficacy of OCA was established in a single phase 3 trial; the phase 3 trial was adequately designed and well-controlled. Data from two controlled dose-ranging, phase 2 trials, of 3 months duration, one with monotherapy, were also submitted, as well as supportive data from multiple nonclinical and phase 1 trials.

The phase 3 trial was a one year trial in 216 patients with three arms; placebo, 10mg and titration from 5mg to 10 mg at 6 months. Enrollment criteria required either ALP to be $> 1.67 \times \text{ULN}$ or $\text{TB} > \text{ULN} < 2 \text{ULN}$. The primary efficacy endpoint for the phase 3 trial was a composite of $\text{ALP} < 1.67 \times \text{ULN}$ and total bilirubin $\leq \text{ULN}$ and at least $\geq 15\%$ reduction in ALP. At month 12 a total of 46% and 47% patients on OCA titration and OCA 10 mg arm respectively achieved the prespecified endpoint, and these were statistically significant relative to placebo. The ALP reduction response is durable as seen in the long-term safety extension trial. Subgroup analyses (disease severity, age, gender) were not conducted due to small sample size. Other exploratory endpoints supported the ALP reduction with improvements in transaminases and markers of inflammation. Overall the trial results were considered robust and sensitively analysis supported the primary analysis, (Section 7.6) both using ALP alone and the prespecified composite endpoint.

In the phase 3 trial 93% of patients were taking UDCA which is reflective of clinical practice, the monotherapy treated patients had a response rate similar to the UDCA treated patients. A 3 month phase 2 trial assessed efficacy of OCA monotherapy, biochemical response of ALP reduction was observed, similar to phase 3 trials results, relative to placebo arm. Based on the combined results from the phase 2 and 3 trials the team recommended approval of the monotherapy indication, however the Applicant has agreed to a PMR for a controlled safety and efficacy trial with monotherapy to gather additional data on these patients (Section 7.8). It was interesting to note that there appeared to be a trend toward less hepatic adverse events in the monotherapy trials, however, the numbers were too small to make conclusions.

The most common adverse event was pruritus, with a positive dose-response relationship noted. As pruritus is frequently present in patients with

PBC, patients with severe pruritus were excluded. Patients were also allowed treatments for pruritus with bile sequestrants and antipruritic drugs or dose modification. It was noted that in the titration arm that there was a decreased incidence and severity of pruritus and the Applicant has elected to recommend that all patients be started on 5 mg with up-titration to 10 mg at 3 months based on biochemical response and tolerability. The team agrees with this dosing regimen. Fatigue is also common with PBC and there is a signal for increased fatigue secondary to OCA. There is a dose response change in the lipid profile of patients taking OCA across clinical trials with all indications. Patients with PBC generally have high HDLc levels with may infer a cardioprotective effect; however this is not well substantiated. Dose dependent HDLc reductions were seen; at month 12 reductions from baseline in mean HDLc was observed in 21% in OCA 10 mg arm, 15% in OCA titration arm and 3% in placebo arm. Some patients had significant decreased in HDLc more than 2 times the standard deviation. Milder increased in LDLc were also seen. These changes are reversible with drug discontinuation. There was no cardiovascular signal (CV) seen with the phase 3 trial, although there was one death secondary to cardiac failure. The phase 4 trial will not be powered to assess CV outcomes but the CV events will be adjudicated and reported (Section 11).

Nonclinical data noted the hepatobiliary system to be the major system of toxicity. With toxicity seen at exposures that may be seen in patients with hepatic impairment on a dose of 10mg daily as used in the clinical trials. In the integrated analysis of the clinical trials there was a dose-response seen for hepatic decompensation events as well as biochemical changes possibly indicative of hepatic injury (Table 14). While these primarily occurred at doses higher than the approved dose of 10mg, they also occurred at 5 and 10 mg doses. While the Applicant initially recommended no dose adjustment for hepatic impairment, the clinical pharmacology team recommended a reduced dose. Because the Applicant only has 5 and 10 mg tablets (b) (4)

Only 20 patients with Child Pugh A cirrhosis were enrolled in the clinical trial, and none with advanced cirrhosis, therefore there is lack of clinical data in patients with cirrhosis. The Applicant has agreed to a PMR for a controlled clinical trial to assess safety and efficacy and steady state PK in patients with cirrhosis with the recommended reduced dose.

The totality of the data support approval of OCA for PBC. The clinical benefit is yet to be established and there is an ongoing phase 4 confirmatory trial. However, the improvements in ALP are deemed by the review team to be reasonably likely to predict clinical benefit in this population with early stage PBC.

If ALP reduction does not predict clinical benefit and the drug is approved then there will be a substantial cost to society and to patients to pay for the treatment and required follow-up. In addition, patients will be exposed to a potential increase in risk for cardiovascular adverse outcomes related to lowering of HDLc. Some patients may require additional treatments to control pruritis and some patients may have events of liver injury associated with OCA. If ALP reduction does predict clinical benefit and the drug is not approved the > 40% of PBC patients who are intolerant or inadequately responsive to UDCA will continue to have progressive disease with poor outcomes resulting in death or liver transplant. This was discussed at an Advisory Committee Meeting on April 7th, 2016 and the committee agreed with use of the ALP biomarker

for accelerated approval of OCA for PBC. The team is in agreement that the risk/benefit for approval based on the surrogate biomarker favors approval.

The Applicant as agreed to expand enrollment in the phase 4 trial to include patients with all stages of PBC. The Division will work with the Applicant on the design specifics of this trial and the other PMRs. Of note, it appears that while ALP is reasonably likely to predict benefit in patients with early stage PBC, as the disease progresses TB may be a better marker of outcomes. Therefore, additional analysis of the PBC Global data sets will be performed to address this question and to identify best endpoints for different subpopulations with PBC. The labeling will include warnings and precautions about the potential for drug induced liver injury, dyslipidemia and pruritus and recommendations for monitoring patients.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| <p><u>Analysis of Condition</u></p> | <ul style="list-style-type: none"> • Primary biliary cholangitis/cirrhosis (PBC) is a chronic, slowly progressive autoimmune, cholestatic liver disease characterized by inflammatory destruction of interlobular and septal bile ducts. The disease is heterogeneous in presentation, both in symptoms and time to progression of disease. • PBC predominately affects women; ratio of women to men is 10:1, typical age of diagnosis is 40-60 years of age • PBC is a rare disease with an incidence of PBC in the U.S. is 4.5 per 100,000 women and 0.7 per 100,000 men (PBC is known to be more common in women). The prevalence was estimated at 65.4 for women and 12.1 for men per 100,000. PBC affects approximately 1/1000 women over the age of 40. • In untreated patients the 5, 10 and 15 year survival is 79%, 59% and 32% respectively. In the ursodeoxycholic acid (UDCA) responsive patients it is 90%, 78%, and 66% respectively. • Other conditions such as osteopenia/porosis, hyperlipidemia, and fat soluble vitamin deficiency are also common in patients with PBC. • Fatigue and pruritus are the two most common symptoms in PBC patients earlier in the disease course and can be disabling. If patients present with either symptom the prognosis/outcomes are worse than | <p>PBC is a slowly progressive, serious and rare liver disease that affects primarily women with a typical age of onset of 40-60 years. Patients eventually progress to liver cirrhosis, liver failure, hepatocellular cancer and death or liver transplant. The phenotype is variable with some patients being fairly asymptomatic, and some patients experiencing severe and debilitating symptoms, such as severe pruritus, fatigue, and malnutrition. In addition, patients also frequently suffer from the symptoms of other co-existing autoimmune diseases. The time course to progression is also variable; risk factors for worse prognosis are male sex and younger age at diagnosis.</p> |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | <p>for patients without symptoms.</p> <ul style="list-style-type: none"> • Extra-hepatic symptoms are common, such as other autoimmune diseases. The most common are Sicca syndrome (75%), Sjogren’s syndrome (34%), thyroid disease (13%), any autoimmune disease (33-55%) etc. • The disease is more aggressive in patients <30 years of age at diagnosis and in men and is less responsive to UDCA treatment. | |
| <p>Current Treatment Options</p> | <p>Ursodeoxycholic acid (UDCA) was approved by the FDA in 1997 for PBC, using composite endpoints of clinical benefit and biochemical changes. Currently UDCA is the only medical treatment available. Overall UDCA has a good safety profile. Non-cirrhotic PBC patients who achieve a biochemical response to UDCA appear to have survival comparable to that of a healthy population. However, there is no consensus on responder criteria. ALP and TB have been the biomarkers used most frequently in assessing prognosis and response.</p> <p>About 40% patients achieve inadequate biochemical response with UDCA and continue to progress to cirrhosis and liver failure.</p> <p>A small percentage of patients do not tolerate UDCA mostly secondary to GI symptoms or hair loss. Data is lacking on the percentage of patients who are intolerant, but it is probably < 8%.</p> <p>Patients with advanced disease or cirrhosis do not respond as well to UDCA. Patients who do not respond to UDCA and continue to progress and develop liver failure or hepatocellular cancer requiring liver transplantation (LTx) (if eligible) or succumb to death. PBC is one of top 6 indications for LTx in US. Even with liver transplantation PBC recurrences are noted, although the progression of PBC in recipient liver is very slow, up to 10-43% incidence of PBC recurrence at 15 years post-transplant is reported.</p> | <p style="text-align: right;">(b) (4)</p> <p>There is an unmet medical need in patients with PBC who are:</p> <ul style="list-style-type: none"> Intolerant to UDCA Have an inadequate response to UDCA Advanced disease <p>The treatment armamentarium would greatly benefit from new safe and effective therapies for these patients</p> |

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| <p><u>Benefit</u></p> | <p>Efficacy Results</p> <ul style="list-style-type: none"> The efficacy of OCA was established in one phase 3 trial; the phase 3 trial was adequately designed and well-controlled trial. The safety and efficacy of monotherapy was assessed from additional two phase 2 trials. Data from the three trials was accepted for this review process, with total of 440 patients enrolled across all trials, as well as supportive data from multiple nonclinical and phase 1 trials. The trials varied in treatment duration and dose. Patients were enrolled on basis of elevated alkaline phosphatase (ALP); the overwhelming majority of patients had normal total bilirubin (TB) and normal albumin and thus they were early stage disease by the Rotterdam criteria. (early stage - normal total bilirubin and albumin, moderately advance stage - either TB abnormal, advanced stage – both abnormal). The phase 3 trial was a 12 month trial in 216 patients with three arms, placebo, 10 mg and titration from 5 mg to 10 mg. The primary efficacy endpoint for the phase 3 trial was a composite of ALP <1.67 X ULN and TB ≤ ULN and at least ≥ 15% reduction in ALP. However, since 92% patients in the phase 3 trial had TB within normal reference range at baseline the main driver of the efficacy results was reduction in ALP. <p>Phase 3 results</p> <ul style="list-style-type: none"> At month 12 a total of 46% and 47% patients on OCA titration and OCA 10 mg arm respectively achieved reduction in ALP >1.67 x ULN and at least ≥ 15% reduction in ALP, and these were statistically significant relative to placebo (10%). Of the 18 patients who had elevated ALP and TB at baseline one 1 of 4 patients in the titration arm, 2 of 7 patients in OCA 10 mg and 0 of 7 patients in placebo arm achieved the composite endpoint. The ALP reduction response is durable as seen in the long term safety | <ul style="list-style-type: none"> The totality of the data submitted supports that OCA is effective in reducing ALP levels in patients with PBC. The overall safety of the drug was good especially considering the risk to the population to be treated. Limitation of data: <ul style="list-style-type: none"> The phase 3 trial enrolled 90% patients with early stage disease. There were 10% patients enrolled with moderately advanced disease (as defined by Rotterdam criteria) or in patients with decompensated cirrhosis. There is limited data in patients using OCA as monotherapy. <p>With the seriousness of the disease and the overall good safety profile no limitations of use will be placed in the labeling and dosing recommendation for patients with hepatic impairment will be included. A PMR will be performed in patients with hepatic impairment.</p> <p>The analysis of the PBC study group data supported that a reduction in ALP predicted clinical benefit for patients treated with UDCA, and therefore supported the conclusion that ALP reduction in this population is reasonably likely to predict clinical benefit for OCA treatment.</p> <ul style="list-style-type: none"> The confirmatory trial is ongoing and until the results are analyzed the clinical benefit of reduction in ALP as surrogate is yet to be established |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | <p>extension trial in data submitted to a cutoff point of up to 30 months.</p> <ul style="list-style-type: none"> • Subgroup analyses (disease severity, age, gender) were not conducted due to small sample size. • All 3 controlled clinical trials demonstrated reduction in ALP, which was seen as early as 2 weeks and the response was durable and sustained at 3 month in both phase 2 trials and at 12 months in the phase 3 trial. • Notably, in a 3 month phase 2 trial to assessed efficacy of OCA monotherapy, biochemical response of ALP reduction was observed, similar to phase 3 trials results, relative to placebo arm. • Patients enrolled in the North American sites showed a down trend in ALP but did not reach statistically significant reduction in ALP in either OCA treatment arm. • The secondary endpoints were TB, GGT, AST and ALT. The total bilirubin also reduced albeit in this was seen in few patients with OCA treatment. A statistical significant number of patients treated with OCA achieved GGT reduction, and is a supporting evidence for reduction in cholestasis. Aminotransferases (ALT and AST) reduction was also statistically significant in the OCA treated group and is supportive of reduction of the hepatocellular damage. Additionally, there was reduction (but not normalization) of IgM in the OCA treated group which was statistically significant compared with placebo group. IgM is specifically elevated in PBC. <p>Surrogate Endpoint Discussion</p> <ul style="list-style-type: none"> • The Division had previously agreed with the Applicant to allow use a composite endpoint of reduction in TB and ALP as a surrogate endpoint, based on data published by the Global PBC study group, which conducted retrospective analyses on 4,845 PBC patients and found ALP and TB as a composite endpoint prognosticates death and liver transplantation. In light of the population enrolled and the need | |

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| | <p>to evaluate data to support the likelihood of ALP reduction alone being reasonably likely to predict clinical benefit in this population of PBC patients the Division requested the data sets from the Global PBC study group. These data sets were submitted as a DMF file and were not accessible to the Applicant.</p> <ul style="list-style-type: none"> • FDA identified a subset of patients that matched the trial population (baseline ALP >1.67 X ULN, UDCA concomitant usage, and early stage disease as per Rotterdam criteria). Using these same matching criteria resulted in 181 patients identified from the phase 3 trial. • Multiple thresholds were tested and the following thresholds were identified as best predictive: <ul style="list-style-type: none"> ○ if the baseline ALP ≥ 2 X ULN then patient was designated as responder when patient achieved both ALP < 2.0×ULN and decrease $\geq 40\%$ ○ AND if the patients baseline ALP was ≥ 1.67 X ULN then the patient was designates as responder if patient achieved both ALP < 1.67×ULN and a decrease $\geq 15\%$. • For the FDA derived threshold the C-statistics were (0.68-0.70) and Hazard ratio were (2.54-2.68) which were better when compared with C-statistics of 0.64-.068 and HR of 1.82-2.42 for threshold the prespecified endpoint It was also noted that multiple different thresholds all supported the efficacy results. FDA modified exploratory analyses of ALP reduction was statistically significant for the OCA treated group (43% and 38% for OCA 10 mg and OCA titration group respectively) compared to 5% response in placebo arm. <p>Advisory Committee Meeting</p> <ul style="list-style-type: none"> • An Advisory Committee meeting was held on April 7th 2016 to query whether the committee assessed ALP was an appropriate surrogate that is reasonably likely to predict clinical benefit. Assessing the data | |

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| | <p>in totality the AC member voted 17-0 in favor of OCA approval on basis of ALP reduction, as they considered ALP is used as a biomarker for diagnosing, following the progression of the disease and there is biological plausibility of ALP as a surrogate in PBC.</p> | |
| <p><u>Risk</u></p> | <ul style="list-style-type: none"> • The safety database for OCA includes all patients from two phase 2 and one phase 3 trial. Additional safety databases reviewed included trials conducted in healthy volunteers (PK/PD trials) and non-alcoholic steatohepatitis (NASH) trials. The safety profile demonstrated for OCA was consistent across the phase 2 and 3 trials. • Dose dependent increase in pruritus as well severe pruritus was observed. Incidence of pruritus was 38% in placebo, 56% in OCA titration arm and 68% in OCA 10 mg arm. Incidence of severe pruritus was as follows 7% in placebo, 19% in OCA titration arm and 23% in OCA 10 mg arm. There were 7 discontinuations due to pruritus in OCA 10 mg arm, one discontinuation in OCA titration arm, compared to zero discontinuations due to pruritus in the placebo arm. The incidence of pruritus was higher in patients with baseline ALP >3 X ULN. • Dose dependent increase in the incidence of fatigue was seen: 14% placebo patients, 16% patients in placebo arm and 23% patients in OCA 10 mg arm experienced fatigue. • Dose dependent HDLc reductions were seen across all clinical trials. IN the phase 3 trial at month 12, reductions from baseline in mean HDLc was observed in 21% in OCA 10 mg arm, 15% in OCA titration arm and 3% in placebo arm. • AEs of pruritus, fatigue and HDLc reductions were reversible on OCA discontinuation. • The majority of patients were female and white. Differences in the incidence of the adverse events were not discernable across different sub-populations (age, gender, race, baseline UDCA use, baseline total bilirubin) as the imbalance in the sample size precludes a | <ul style="list-style-type: none"> • Overall the safety of OCA use is well characterized in early stage PBC population. • Pruritus and fatigue appear to be worsened in some patients taking OCA and could limit use in some patients. • Reduction in HDLc may over time increase the risk for cardiovascular events. • There were no major/serious safety concerns • Data of longer duration of OCA use are required to understand the implications of HDLc lowering on cardiovascular events • OCA can result in liver injury at high exposures as seen in nonclinical studies and in early phase trials with higher doses. Patients with impaired hepatic function can have much higher exposures and a reduced dose has been recommended. More data is needed in patients with hepatic impairment, however secondary to the seriousness of the disease and lack of treatment options for these patients, and the reduced dose recommended, no limitation of use will be placed in the labeling for these patients. • As is a common pattern in many different chronic liver diseases, ALP may be a better marker of progression of disease and |

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| | <p>meaningful interpretation.</p> <ul style="list-style-type: none"> • Drug-drug interactions were limited (Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates) • Potential for Liver Injury: • Nonclinical data noted the hepatobiliary system to be the major system of toxicity. The NOAEL from the chronic toxicity study in rats and dogs were estimated to produce systemic exposures approximately 2.3 and 12 times those in humans at the maximum recommended human dose respectively • At doses of 25 mg and 50 mg (which are higher than the to-be-approved doses of 5 and 10mg), higher rates of hepatic decompensation events were observed (new onset jaundice, ascites, and PBC flare) as well as biochemical changes possibly indicative of hepatic injury. OCA undergoes enterohepatic circulation and it and its conjugates have a very long half-life • 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 | <p>response to treatment in early phases of PBC. As the disease progresses the ALP levels may gradually decrease as the bilirubin increases making it an inadequate marker for trials in patients with advanced disease.</p> |
| <p><u>Risk Management</u></p> | <ul style="list-style-type: none"> • Pruritus and increased fatigue are common but non-serious AEs that can usually be managed with dose manipulation or addition of bile binding resins or antipruritic agents. Some patients may require discontinuation. • Reductions in HDLc have of unknown but the potential to increase risk for cardiovascular AEs. Reductions are variable between patients. HDLc should be monitored during therapy. • This drug is PREA exempt secondary to orphan status and this disease does not occur in children. • The safety of OCA has not been established in pregnant women or during breast feeding. | <ul style="list-style-type: none"> • Dose adjustment should be performed in patients with hepatic impairments, and in instances of disease progression. Close monitoring patients with hepatic impairment is also recommended in the labeling. • PMR for a placebo-controlled trial to gather more data on OCA as monotherapy • PMR for more data on patients with hepatic impairment. • Modify current phase 4 (postmarketing trial) to include patients with all stages of |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
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| | <ul style="list-style-type: none"> • Close monitoring of patients with advanced PBC disease or cirrhosis should be performed secondary to the lack of data in these patients and the potential for higher exposures and liver injury. • As post-marketing trial to assess steady state PK and safety and efficacy in patients with advanced PBC and patients with cirrhosis will be performed as part of accelerated approval • There is inadequate data on use of OCA as monotherapy and additional data will need to be collected as part of the post-marketing requirements under accelerated approval. | <p>disease.</p> <p style="text-align: right;">(b) (4)</p> <p>• Labeling to reflect need to monitor patients lipid profile and monitor patients liver enzymes for potential liver injury signals</p> |

2. Background

2.1 Product Information

Obeticholic acid/OCALVIA/OCA is a new molecular entity and is a modified bile acid. It is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine (also expressed in kidney, adrenal glands, and adipose tissue). OCA is derived from chenodeoxycholic acid (CDCA), but is approximately 100-fold more potent at the FXR due to the addition of a single α -ethyl arm in the 6-carbon position. UDCA is an epimer of CDCA. While structurally similar to CDCA or OCA, UDCA has no significant FXR agonist effects, UDCA acts through post-translational mechanisms. The trade name proposed by the Applicant is OCALIVA which is acceptable to the FDA. OCA will be used to refer to obeticholic acid/OCALIVA throughout this document.

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

1. Increased synthesis of fibroblast growth factor-19 (FGF-19);
2. Induction of transcription factor heterodimer protein (SHP); and
3. Repression of cholesterol 7- α -hydroxylase (CYP7A1) expression and bile acid synthesis

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

CDTL Comment:

This is the primary therapeutic rationale for FXR agonists use in PBC (cholestatic liver disease). OCA does not target the basic immunopathogenesis of PBC; however, it appears OCA acts predominantly by its choleric action. Although the Applicant has

(b) (4)

On literature review it was noted that transgenic mice overexpressing human fibroblast growth factor 19 (FGF19) in skeletal muscle had elevated hepatic alpha-fetoprotein mRNA as early as 2 months of age, and hepatocellular carcinomas were evident by 10 months of age. This was not noted in the nonclinical carcinogenicity studies, however there is a potential for increased risk.¹²

2.2 Proposed Indication and Dose

The Applicant has proposed an indication for the treatment primary biliary cirrhosis (PBC)

(b) (4)

The proposed dose is 5 mg orally, daily with up titration to 10 mg daily after 3 months of treatment, based on biochemical response and tolerability. The Applicant proposed to use a surrogate biomarker of improvements in alkaline phosphatase (ALP) and total bilirubin (TB) to evaluate efficacy under the accelerated approval pathway. See discussion on the definition of biochemical response

(b) (4)

2.3 Therapeutic Context

Primary biliary cholangitis or cirrhosis (PBC) is a rare and progressive autoimmune, cholestatic liver disease that primarily affects women (10:1) and typically presents at age 40-60 years. It is characterized by inflammatory destruction of interlobular and septal bile ducts. The disease is heterogeneous in presentation, both in symptoms and time to progression of disease. It is frequently diagnosis by screening liver chemistries, with an elevated alkaline phosphatase (ALP) noted that prompts an evaluation. PBC is a rare disease with prevalence of 40.2/100,000 in US and 39.2/100,000 in Europe. In untreated patients the 5, 10 and 15 year survival is 79%, 59% and 32% respectively. In the ursodeoxycholic acid (UDCA) responsive patients it is 90%, 78%, and 66% respectively. Other conditions such as osteopenia/porosis, hyperlipidemia, and fat soluble vitamin deficiency also common in patients with PBC.

The liver injury is mediated by inflammatory infiltrate (plasma cells, lymphocytes, mononuclear cells etc.), that causes necrosis of small intrahepatic bile ducts leading to bile duct loss (ductopenia) and bile stasis. Bile salts have detergent like properties and causes damage to both bile ducts as well as hepatic parenchymal structures. The damage caused by inflammatory infiltrate and bile stasis

¹ Nicholes, K, et al., A mouse model of hepatocellular carcinoma: ectopic expression of fibroblast growth factor 19 in skeletal muscle of transgenic mice, *AmJ Pathol*, 202, Jun;160(6):2295-307.

² Miuram S, et al., Fibroblast growth factor 19 expression correlates with tumor progression and poorer prognosis of hepatocellular carcinoma, *BMC Cancer*, Feb 2012, 12:56, DOI: 10.1186/1471-2407-12-56.

leads to fibrosis and cirrhosis. Bile salts are required in absorption of fat and fat soluble vitamins, decrease of bile flow to intestines causes malabsorption of nutrients and micronutrients.

Fatigue and pruritus are the two most common symptoms in PBC patients earlier in the disease course and can be disabling. If patients present with either symptom the prognosis/outcomes are worse than for patients without symptoms. Extra-hepatic symptoms are common, as are other autoimmune diseases. The most common are Sicca syndrome (75%), Sjogren’s syndrome (34%), thyroid disease (13%), any autoimmune disease (33-55%) etc. The disease is more aggressive in patients <30 years of age at diagnosis and in men and is less responsive to UDCA treatment.

Cirrhosis eventually leads to portal hypertension which causes hemodynamic alterations such as increased portal pressures, portal-systemic shunting, splanchnic vasodilation and peripheral vasoconstriction, increased cardiac output etc. Therefore in advanced stages of disease, in addition to the inflammation, bile duct loss and bile stasis mediated damage; progressive injury is accelerated by onset of portal hypertension and its complications (esophageal variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites etc.) which further speeds up the process of liver failure.

There is one approved treatment for PBC. Ursodeoxycholic acid (UDCA) was approved by the FDA in 1997 using composite endpoints of clinical benefit and biochemical changes. Overall UDCA has a good safety profile. Non-cirrhotic PBC patients who achieve a biochemical response to UDCA appear to have survival comparable to that of a healthy population. ALP and TB have been the biomarkers used most frequently in assessing prognosis and response in PBC. There is no consensus on responder criteria. The most commonly used staging system is the

Rotterdam Criteria:

| | |
|-----------------------------|---------------------------|
| Early disease | normal ALP and TB |
| Moderately advanced disease | either ALP or TB abnormal |
| Advanced Disease | both ALP and TB abnormal |

CDTL Comment:

Note that these criteria are different that staging for liver disease in general. In general, liver disease is divided into pre-cirrhotic and cirrhotic stages and cirrhosis is defined several ways. Patients with cirrhosis can be broadly classified as compensated or uncompensated. Cirrhosis is also classified by stage, see Table 1. The Child-Pugh classification of stages of cirrhosis, A, B and C is based on TB, albumin, prothrombin time, ascites and hepatic encephalopathy. The model for end stage liver disease (MELD) score which is used to classify risk for short term mortality uses INR, serum creatinine and TB. MELD is used as the main criteria for listing

for liver transplant with a MELD cutoff of greater than 14 indicating the risk of transplant is lower than the risk of death. None of these scores matches with the Rotterdam criteria and patients could have cirrhosis at any stage in the Rotterdam system, though one would expect the majority of patients in early stage to be noncirrhotic with increasing incidence of cirrhosis as you move to more advanced stages.

Table 1: Stages of Cirrhosis

| Stage | Description | 1 year mortality | % exiting to more advanced stage |
|-------|---|-------------------------|----------------------------------|
| 1 | compensated, absence of esophageal varices | 1.5% | 11.9% |
| 2 | compensated, with esophageal varices | 2% | 12.2% |
| 3 | Variceal bleeding, no other decompensation events | 10% | 21% |
| 4 | Ascites, jaundice or encephalopathy | 21% | 10% |
| 5 | More than one decompensation event | 27% (87% at 5 years) | |

Source: Gennaro D’Amico, Natural History and Stages of Cirrhosis R. de Franchis and A. Dell’Era (eds.), Variceal Hemorrhage, DOI 10.1007/978-1-4939-0002-2_2, © Springer Science+Business Media New York 2014

Approximately 40% of patients have an inadequate response to UDCA and a progressive course to liver failure and death. A small percentage of patients are intolerant to UDCA, mostly secondary to gastrointestinal side effects for hair loss. For these patients there is an unmet medical need for safe and effective treatments.

2.4 Regulatory Background

Effective on January 27, 2006, the Applicant initiated clinical development of OCA, under IND 63,307 for treatment of PBC. This is a new molecular entity and is not currently marketed in the United States or internationally. The Applicant has also submitted a marketing application to the EU for this product for the same indication. This is the first submission for this NDA.

The drug is (b) (4) (b) (4)

IND 63,307 was submitted on 27 January 2006, received Orphan drug designation on 9th April 2008; fast track designation in the treatment of PBC on May 27, 2014; Rolling review was granted on 18 November 2014. Presubmission regulatory activities related to this submission included approximately 5 formal face-to-face meetings between the Applicant and FDA. In addition, there were a number of teleconferences and written correspondences exchanged during the development 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). The Applicant subsequently leveraged the results from this independent study to construct the composite endpoint used in the pivotal phase 3 study (747-301).

The SAP for the pivotal trial analyses was designed in consult with DGIEP with a follow up meeting to finalize the plan held on October 2, 2013. The meeting also included a discussion of the data requirements for accelerated approval and next steps for the development of OCA in the treatment of PBC. Based on DGIEP guidance, it was understood by Intercept that the acceptability of the lone pivotal study to support accelerated approval is dependent on DGIEP's review of the results from this study and the determination as to whether the proposed surrogate endpoint is reasonably likely to predict clinical benefit, which is critically

dependent on DGIEP’s review of the Global PBC Study. Per 21 CFR 314.510, the program would also need to be supported by a confirmatory clinical outcomes study underway prior to obtaining accelerated approval. As such, two Type C meetings to discuss the design of this proposed confirmatory outcomes study were held on January 29, 2014 and July 22, 2014. Key discussion topics included the proposed subject population, primary endpoint, study design and planned statistical analyses. As agreed during these meetings, Intercept addressed and incorporated DGIEP’s comments, and the first version of the final confirmatory study protocol and its final SAP were submitted to IND 63,307 on October 9, 2014 (each dated October 3, 2014 and October 7, 2014, respectively). This study (i.e., trial 747-302) is currently open for enrollment in the US and Latin America, and it is in the initiation process in the European Union (EU) and other countries. There was one amendment made to the original protocol on April 29, 2015, and this version was submitted to IND 63,307 on May 6, 2015; there have been no amendments to the SAP.

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

Therefore the Division approached the Applicant and The Global PBC Study Group to obtain access to the data sets from the study group. The PBC Study Group did submit these data sets to the Agency in the form of a DMF file. The Applicant did not have access to the data sets but only the analyses of the data as performed by the PBC Study Group or the Division. (See section 7.2 on page 26 for discussion of the results of the analysis of this data).

2.3 Approval Basis for UDCA

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.³ In the first trial (a 2-year, placebo-controlled trial) the clinical endpoints evaluated in the trial were death, transplant, histologic

³ UDCA Labeling at Drugs@FDA.gov

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 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.

Meta-Analysis of UDCA Trials

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.^{4,5} 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). 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.^{2,6,7}

⁴ 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.

⁵ 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.

⁶ Carbone M, Mellis 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 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.

3. Product Quality

Table 2: Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|--|---------------------|-----------------------------------|
| Drug Substance | Ben Stevens | OMPT/CDER/OPQ/ONDP/DND API/NDBII |
| Drug Product | Hitesh Shroff | OMPT/CDER/OPQ/ONDP/DNDPII/NDPBV |
| Process | Vaikunth Prabhu | OMPT/CDER/OPQ/OPF/DPAII/PABV |
| Microbiology | Vaikunth Prabhu | OMPT/CDER/OPQ/OPF/DPAII/P ABV |
| Facility | Bryan Ryan | OMPT/CDER/OPQ/OPF/DIA/IABIII |
| Biopharmaceutics | Peng (Vincent) Duan | OMPT/CDER/OPQ/ONDP/DB/BBII |
| Regulatory Business Process Manager | Truong Quach | OMPT/CDER/OPQ/OPRO/DRBP MI/RBPMBI |
| Application Technical Lead | Hitesh Shroff | OMPT/CDER/OPQ/ONDP/DNDPII/NDPBV |
| Laboratory (OTR) | Laura Pogue | OMPT/CDER/OPQ/OTR/DPA/PABII |
| ORA Lead | Paul Perdue | OGROP/ORA/OO/OMPTO/DMP TPO/MDTP |
| Environmental Assessment (EA) | James Laurenson | OMPT/CDER/OPQ/ONDP |
| Statistical review of Stability November 5 th , 2015 | Yu-Ting Weng, Ph.D. | Biometrics Division: VI |

3.1 General Product Quality Considerations

Per the QPQ final review (April 19, 2016):

The Applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

Obeticholic acid tablets are manufactured (b) (4) drug product manufacturing process (b) (4)
The tablet manufacturing process and in-process controls proposed by the applicant to produce consistent quality drug product are deemed adequate.

The 5 mg tablets containing 5 mg obeticholic acid are yellow, round, debossed with INT on one side and 5 on the other side. The 10 mg tablets containing 10 mg obeticholic acid are yellow, triangular tablets, debossed with INT on one side and 10 on the other side. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating Opadry II (Yellow) contains polyvinyl alcohol-part hydrolyzed, titanium dioxide, Macrogol (polyethylene glycol 3350), talc, and iron oxide yellow. The drug product is supplied in a 40 cc high density polyethylene bottle containing 30 tablets and it is closed with an induction seal and a 33 mm polypropylene child resistant cap.

The identity, strength, purity and quality of the drug product are assured by the adequate raw material controls, validated manufacturing process and drug product specification.

Based on the stability data submitted 24-month expiration dating period is well justified when stored in the proposed container closure system at 25°C.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the label/labeling issues had not been completely resolved as of 4/19/16

3.2 Facilities Review and Inspection

The Office of Facility and Process has made a final overall manufacturing Inspection “Approval” recommendation for the facilities involved in this application.

3.3 Other Issues

There were no intercenter consults and no device issues involved in this application.

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Melkamu Getie-Kehtie, Ph.D., R.Ph., Staff Fellow, Yiyue Zhang, Ph.D., and Arindam Dasgupta, Ph.D. Lead Pharmacologist Division of Generic Drug Bioequivalence Evaluation (DGDBE), Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion and arranged an inspection of the clinical portion of the following pharmacokinetic study in a review dated November 12th, 2015. Study Number: 747-115 “An Open-Label, Two-Way Crossover Trial to Assess the Biocomparability of Two Tablet Formulations of Obeticholic Acid After a Single Dose in Healthy Adult Subjects” was following the evaluation of the inspectional findings and EIR, the analytical and clinical data from the audited study were found to be reliable. Therefore, we recommend that the analytical and clinical data for study #747-115 be accepted for further Agency review.

From the review of the Methods Verification Report Summary by Danuta Gromek-Woods, Acting Team Lead, Office of New Drug Products (ONDP), Branch V, dated 2/22/2016, “the methods are acceptable for control and regulatory purposes”.

4. Nonclinical Pharmacology/Toxicology

Summary

There were no major nonclinical issues during the review of this package. It was noteworthy that the major signal of toxicity was in the hepatobiliary system.

As abstracted from the review of Tracy Behrsing, Ph.D., primary reviewer and Sushanta Chakder, Ph.D. Supervisor/Team Leader:

The nonclinical safety package for OCA included pharmacology, pharmacokinetics/ ADME/toxicokinetics, single-dose and repeat-dose toxicology, genetic toxicology, carcinogenicity, reproductive and development toxicology, and special toxicity studies.

OCA is a FXR agonist; with EC50 values ~100-fold lower than the natural FXR agonist chenodeoxycholic acid (CDCA). Like endogenous bile acids, OCA is conjugated with the amino acids taurine and glycine. With the exception of the rabbit, OCA is primarily metabolized to the taurine conjugate with minimal or no metabolism to glyco-OCA in nonclinical species (mouse, rat, and dog). In contrast, both the taurine and glycine conjugates are major metabolites in humans, and exposures to the conjugates exceed those to the parent compound. Based on EC50 values, the glycine and taurine conjugates of OCA have potencies at FXR which are similar to the parent compound; and thus, these are considered to be active metabolites.

In repeat-dose oral toxicity studies in rodents and non-rodents, the hepatobiliary system was identified as the primary target system of toxicity. In the 26-week oral toxicity study in rats, treatment with OCA produced changes in clinical chemistry parameters (e.g., increases in ALT, AST, and ALP), increased liver weights, and bile duct hyperplasia with hepatocellular hypertrophy. Clinical signs such as yellow skin were observed in high dose animals (60 mg/kg/day). In the 9-month oral toxicity study in dogs, OCA produced clinical signs of toxicity that could be associated with liver function (yellow discoloration of the skin, mucous membranes, and eyes) and elevated ALT levels. While there were no microscopic changes in the liver in the 9-month toxicity study, histopathological changes were noted in the liver and gallbladder in a shorter duration study in dogs. Increased liver enzymes were also observed in humans at higher doses than 10 mg, proposed for the current indication. Additional primary target organs in the 26-week toxicity study in rats were the large intestine (subacute inflammation) and bone marrow (increased cellularity).

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

CDTL Comment:

Note that the NOAEL for exposures in dogs is 12 times those in humans and that the primary signal is in the hepatobiliary system. While the modeling for the systemic exposures done for patients with moderately advanced and advanced hepatic impairment show exposures up to 17 times that of healthy patients (See Section 5, on page 27). Therefore this corroborates that lower doses should be recommended for patients with hepatic impairment and it is important to monitor these patients closely and adjust dose or discontinue treatment for evidence of liver injury.

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

CDTL Comment:

The information about the increased incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats was conveyed in the labeling.

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

In an oral fertility and early embryonic development study, treatment of male and female rats with up to 50 mg/kg/day OCA did not affect fertility or early embryonic development. The NOAELs for male and female systemic toxicity in this study were 50 and 25

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mg/kg/day, respectively. In an embryofetal development study in rats, 75 mg/kg/day OCA caused decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses. In maternal animals, this dose produced mortality, decreased body weight, body weight gain, and food consumption, and abortion. Therefore, the developmental toxicity observed at this dose may be secondary to maternal toxicity. The NOAEL for maternal toxicity and embryofetal development in this study was 25 mg/kg/day. In an embryofetal development study in rabbits, the NOAEL for maternal and developmental toxicity was 20 mg/kg/day OCA (the highest dose tested). Finally, in a pre- and postnatal development study in rats, there was no evidence of any adverse effect on pre- and postnatal development at oral doses of OCA up to 40 mg/kg/day (the highest dose tested).

The review noted that “from a nonclinical standpoint, this product is approvable for indication proposed”, with the labeling changes as were recommended in the review for changes to sections 8.1 Pregnancy, 8.2 Lactation, 12.1 Mechanism of Action, and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.

Established Pharmacologic Class

In response to a July 29, 2015 Information Request and high-level labeling comments from FDA in the August 28, 2015 Filing Communication-Filing Review Issues Identified, the Applicant submitted proposed revised text for the label (b) (4) Nonclinical review of the Applicant’s proposed established pharmacologic class and sections 8.1, 8.2, 12.1, and 13.1 is provided below.

Obeticholic acid is a first-in-class NME. The Applicant has proposed the term “Farnesoid X receptor agonist” as the established pharmacologic class for obeticholic acid. The proposed established pharmacologic class, which is based on the drug’s mechanism of action, is acceptable.

5. Clinical Pharmacology

Table 3: Division of Pharmacometrics and Clinical Pharmacology 3 Review Team

| Division | Reviewer |
|---------------------------|--|
| OCP Reviewers | Elizabeth Shang, Ph.D. (Primary) Shen Li, Ph.D. (In vitro study review) |
| Pharmacometrics Reviewers | |
| PBPK Reviewer | Dhananjay Marathe, Ph.D. Yuching Yang, PhD. Ping Zhao, Ph.D. |
| OCP Team Leader | Sue-Chih Lee, Ph.D. |
| PM Team Leader | Nitin Mehrotra, Ph.D. |
| PBPK Lead | Ping Zhao, Ph.D. |

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

The clinical studies conducted in patients with PBC consist of two phase 2 and one pivotal phase 3 studies. The phase 2 studies evaluated dosing of 10, 25 and 50 mg QD dosing. The phase 3 study 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).

5.1 Executive Summary

As Extracted from the Executive summary of the Division of Pharmacometrics and Clinical Pharmacology 3 review:

OCA is not metabolized by CYP enzymes. Major active metabolites (glyco-OCA and tauro- OCA) in human plasma are amino acid conjugates. After oral administration of 25 mg [14C]- OCA, about 87% is excreted in feces. Urinary excretion is less than 3%.

The key questions raised during the review of this NDA are given below along with the OCP review team’s recommendations:

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

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

It is recommended that the Applicant use uncorrected values of ALP and total bilirubin for the primary efficacy analysis as some of the total bilirubin data were not corrected in the database.

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

Yes, based on the dose dependent increase in incidences of pruritus and better tolerability profile with time with a lower starting dose, Applicant’s proposal to start dosing at 5 mg QD (once daily) is appropriate. Although, patients in the phase 3 trial were up-titrated at 6 months, the proposal of up-titration of dose at 3 months is supported by the clinical data that showed that the trend of reduction in ALP saturated at 3 months upon 5 mg once daily dosing and there was minimal further decrease in ALP from 3 months to 6 months and beyond with the same dose at the population level. Further, the median time to onset of severe pruritus was < 2 weeks and all of the discontinuations due to pruritus in the 10 mg QD arm occurred within the first three months. Thus, the duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability issues. The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12. Also there were some subjects who were responders at month 6,

but became non-responders by month 12, possibly due to disease progression, with continued dosing of 5 mg QD. These patients might also benefit from up-titration to 10 mg QD. The physicians should continue to evaluate biochemical response (reduction in ALP) longitudinally and utilize the up-titration rule at ≥ 3 months from the treatment initiation.

3. Are dose adjustments required for patients with hepatic impairment?

Yes, given that the hepatic impairment (moderate and severe) resulted in several fold (4- to 17 fold) increase in plasma exposures of OCA as compared to healthy volunteers in the dedicated study with a single 10 mg dose, the following dosing schema is recommended. See discussion in Section 5.3 on page 16 below.

4. Is there evidence for approval of OCA as a monotherapy in adult subjects unable to tolerate UDCA?

Yes, there is evidence of activity of OCA to support its approval in a monotherapy setting 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 good responder rate (38%) for monotherapy at 3 months and this responder rate was comparable to that achieved with combination therapy with UDCA (Table 12). Also there was marked reduction in ALP biomarker with monotherapy and this change was statistically significant ($p < 0.0001$) (Figure 14). Based on this evidence, use of OCA as a monotherapy for subjects who are unable to tolerate UDCA seems reasonable.

5. Should there be consideration for discontinuation of OCALIVA for lack of efficacy and, if yes, when?

Possibly, the consideration could be given for discontinuation of OCALIVA for the subjects who do not show response of reduction in alkaline phosphatase if the benefit-risk is unfavorable.

Currently there is not enough evidence to show how the long term efficacy of transplant-free survival and overall survival would transpire for subjects who do not show response of reduction in alkaline phosphatase with OCALIVA. This uncertainty in long term efficacy should be weighed against the possible unfavorable lipid profile (decrease in HDL) and its relation to possible cardiovascular risk due to continued treatment with OCALIVA. Based on the evidence from Phase 3 study, the reviewers propose that the physicians could consider possible discontinuation of drug if there is a lack of clinically meaningful response (reduction in ALP) after the subject is on a stable dose of OCALIVA for ≥ 6 months. There is currently an ongoing Phase 3 extension trial with continued dosing of OCALIVA 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 anti-fibrotic beneficial effect of OCALVIA in order to consider continuation of therapy in the absence of ALP response. This issue will be discussed at the GIDAC (Advisory Committee) meeting and the discussion at the meeting will be considered for informing our final recommendations.

6. Is there potential for OCA to affect the pharmacokinetics of drugs that are CYP1A2 substrates?

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

5.2 General clinical pharmacology, including absorption, food effects, bioavailability, metabolism and excretion.

Obeticholic acid/OCALVIA/OCA is a modified bile acid derived from chenodeoxycholic acid. Like other bile acids it is conjugated to glyco-OCA and tauro-OCA and like other bile acids, OCA and its conjugates 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.

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 effect study showed that plasma exposure of OCA and glyco-OCA were ~15% higher and tauro-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.

(b) (4)

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.

OCA is not metabolized by CYP enzymes. Major active metabolites, glyco-OCA and tauro-OCA, are present in the plasma at much higher concentrations (~14- and ~12-fold, respectively) compared to the parent drug. Following an oral administration of 25 mg [14C]-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.

5.3 Critical intrinsic factors potentially affecting elimination: age, gender, hepatic impairment, and renal impairment.

Gender, age, and race had no impact on the pharmacokinetics of OCA based on the pop-PK analysis.

Body weight was a significant predictor of OCA pharmacokinetics, with lower OCA exposure expected with higher body weight. The median AUC for a 40 kg subject is expected to be 50% higher and median AUC for a 134 kg subject is expected to be 43% lower compared to the AUC for a typical 67 kg subject. 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 IC50 for efficacy (reduction in ALP) after daily administration of OCA at 5 mg and 10 mg doses. Also in the Phase 3 study, for the subjects with 5 mg QD starting dose, 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.

Renal Impairment

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 m²). However, patients with eGFR <50 mL/min/1.73 m² were not enrolled in the study. The effect of severe renal impairment on the systemic exposure to total OCA is unknown.

Hepatic Impairment

The sponsor performed a single dose hepatic impairment study in patients with cirrhosis of various etiologies. The systemic exposure (AUC_{0-9 days}) to total OCA is 1.1-, 4.2-, and 17.3-fold in patients with mild, moderate and severe hepatic impairment, respectively, when compared to healthy controls after a single dose of 10 mg OCA.

There was no apparent association of change of free fraction (%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.

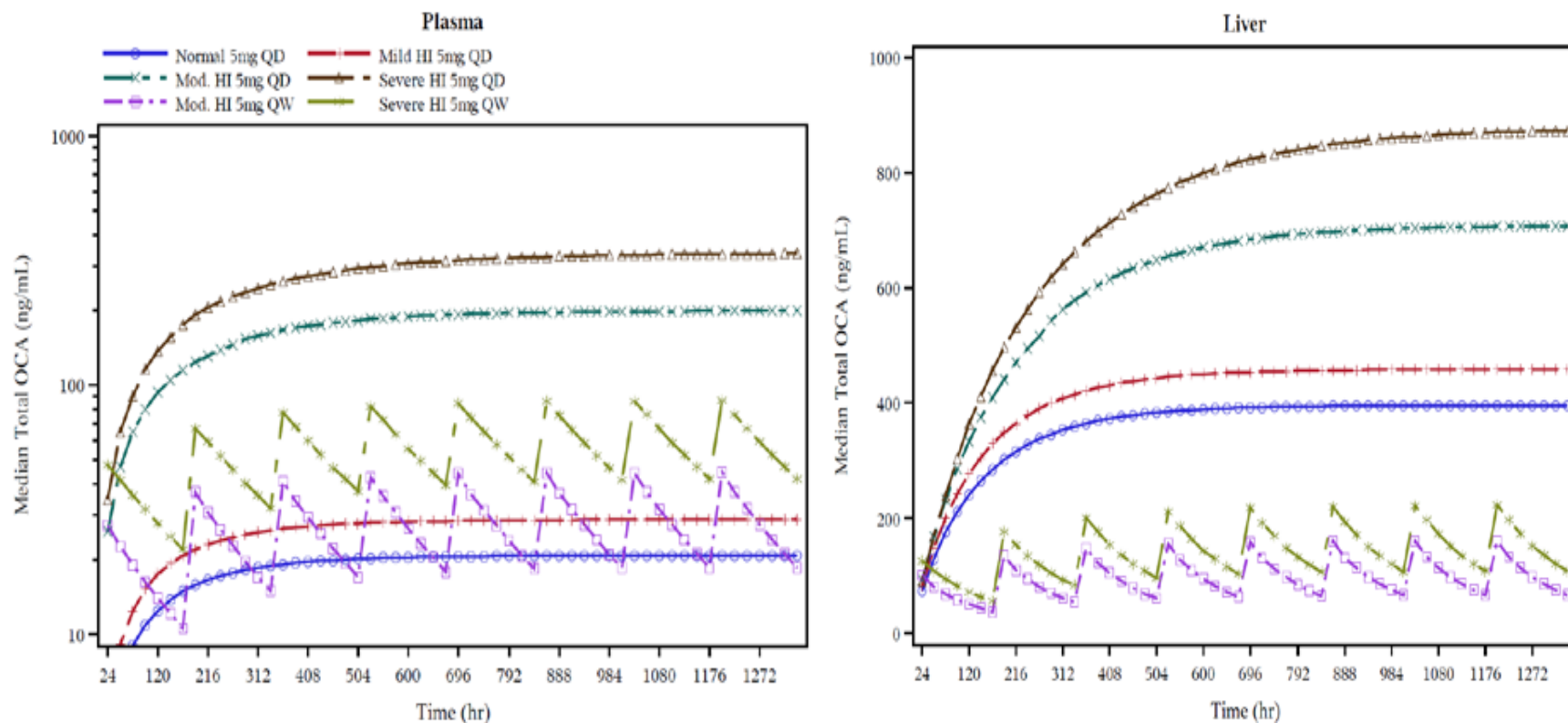
The Sponsor developed a physiologic PK model to quantify the fold changes in liver concentrations of OCA and its conjugates under hepatic impairment scenario. The details of the physiologic PK model can be found in the PBPK model review in the Appendix to the clinical pharmacology review. Table 4 shows the model predicted steady state C_{avg} values for plasma and liver concentrations in subjects with normal hepatic function and subjects with mild/moderate/severe hepatic impairment with different dosing regimen. With the dosing regimen of 5 mg QD, the steady state plasma concentrations (plasma C_{ss, avg}) in moderate and severe hepatic impairment would be 9- and 17-fold and steady state liver concentrations (liver C_{ss, avg}) would be 1.7- and 2.3-fold compared to normal hepatic function. See Figure 1, below.

Table 4: Predicted steady state C_{avg} 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-95 th] | 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-95 th] | 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] |

From FDA clinical pharmacology review Table 10: Source Data: Adapted from Sponsor’s response to Clinical Pharmacology information request

Figure 1: Predicted plasma and liver concentrations of total OCA in subjects with different categories of hepatic impairment with 5 mg QD dosing and in subjects with moderate/severe hepatic impairment with 5 mg QW dosing



From FDA clinical pharmacology review Figure 11: Source Data: Analysis of simulation dataset submitted by the Sponsor in response to Clinical Pharmacology information request

CDTL Comment:

Note from the nonclinical toxicology studies the NOAEL from the 9-month repeat-dose toxicity study in dogs (15 mg/kg/day) was estimated to produce systemic exposures approximately 12 times those in humans at the MRHD and that the primary signal is in the hepatobiliary system. Therefore, the exposures expected in the patients with moderately advanced and advanced cirrhosis has the

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potential to lead to liver injury and increased incidence of other adverse events. This may explain the signal seen for hepatic related adverse events and liver biochemical changes seen in the pooled data. The reduced dose for patients with hepatic impairment should increase the safety for these patients, but these patients should be monitored closely at initiation and during treatment.

From the clinical pharmacology review:

It is worth noting that the Applicant had proposed no dose adjustment for hepatic impairment citing that despite higher systemic plasma exposure levels of OCA in patients with hepatic impairment, liver exposure was predicted to be similar (~2-fold) to healthy controls based on their physiologic pharmacokinetic model.

However, 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, and 50% of severe pruritus onset occurred within 2 weeks of dose initiation, initial dosing regimen to match exposures to normal (no or mild hepatic impairment) PBC subjects will likely avoid potential safety/discontinuation issues and allow identification of subjects who may qualify for up-titration. 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 4 and Figure 1). Further up-titration to 5 mg BIW and subsequently to 10 mg BIW (twice a week) depending on tolerability and efficacy can then be followed to further increase the liver concentrations and meet individual efficacy goals.

5.4 Drug-Drug Interactions

Because OCA and its conjugates are FXR agonists, additional effect on transporters and certain CYP enzymes can occur. For example, FXR activation is known to induce BSEP, MRP2/3, and MDR3 and down regulate OATPs, which may impact the pharmacokinetics of other drugs.

In vitro drug-drug interaction potential

Effect of other drugs on OCA:

Because OCA is not a substrate for CYP enzymes, CYP enzyme inhibition/induction by other drugs will not affect the PK of OCA.

Effect of OCA on other drugs:

CYP inhibition: 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, but a potential *in vivo* drug interaction via inhibition of CYP3A4 in the gut cannot be ruled out.

CYP induction: There is low potential for induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes by OCA, glyco-OCA, or tauro-OCA. However, mRNA down-regulation was observed in a concentration-dependent fashion for CYP1A2 and CYP3A4 by OCA, glyco-OCA, and tauro-OCA.

Substrate for transporters: OCA, glyco-OCA, and tauro-OCA are weak substrates for P-gp. Glyco-OCA and tauro-OCA are substrates for ASBT, Ntcp, OAT3, OATP1B1, and OATP1B3. Tauro OCA is also a substrate for BSEP.

Transporter inhibition: There is potential for OCA and its conjugates to inhibit OATP1B1 and OATP1B3, but not other transporters.

Resin binding agents: Bile acid sequestrants, colestevlam and cholestyramine, bind to OCA, glyco-OCA, and tauro-OCA. See additional comment below.

In vivo Drug-drug interactions

Effect on midazolam, a CYP3A substrate

Dose adjustment of CYP3A substrates is not needed when co-administering OCA 10 mg with a CYP3A substrate.

Effect on caffeine, a CYP1A2 substrate

Following multiple doses of OCA 10 mg QD, AUC_{inf} and C_{max} of caffeine increased by 42% and 6%, respectively. Systemic exposures to paraxanthine were minimally decreased. Further increase in systemic exposure to caffeine was noted when multiple doses of 25 mg QD were coadministered with caffeine. The interaction may be due to CYP1A2 down regulation by OCA, thus, therapeutic monitoring and dose adjustment of CYP1A2 substrates may be needed when co-administering OCA with a CYP1A2 substrate (e.g. theophylline) that has a narrow therapeutic index.

Effect on warfarin, a CYP2C9 substrate

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, the maximum INR is decreased by 11.1% (10 mg QD). Monitoring INR when warfarin is co-administered with OCA 10 mg QD and adjusting dose of warfarin accordingly is recommended.

Effect on rosuvastatin, a substrate for OATP1B1, OATP1B3, and BCRP

Following multiple doses of OCA 10 mg QD, AUC_{inf} and C_{max} of RSV increased by 22% and 27%, respectively. AUC_{inf} of N-desmethyl-RSV increased by 1.1% while C_{max} of N-desmethyl-RSV decreased by 1.3%. Similar effect was found at OCA 25 mg QD. Although in vitro study and the known effect of FXR activation point to potential increased exposure to OATP substrates, only a small increase in exposure to rosuvastatin was observed.

Effect of bile acid binding agents on resins (bile acid sequestrants; BAS)

In the phase 3 study, subjects taking a BAS were to stagger their dosing of OCA and UDCA by at least 4 hours. 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.

5.5 Bridging between the formulation(s) tested in clinical studies and the to-be-marketed formulation.

Four formulations were used in the clinical development program of OCA. Formulation bridging studies were conducted between Formulations A and D as well as between Formulations B and D as Formulation B was used in the pivotal Phase 3 study. (b) (4)

The design of the two formulation bridging studies is identical. A single dose two-way crossover design examining the bioequivalence (BE) of the two 10 mg formulations is employed.

The capsule formulation is bioequivalent to the to-be-marketed formulation. However, the C_{max} of OCA from the to-be-marketed formulation is (b) (4) than the clinical tablet. The upper bound of the 90% CI of geometric mean ratio exceeded 125%, indicating that C_{max} of the two formulations are different. However, (b) (4)% difference in C_{max} of OCA is not considered clinically meaningful as the conjugates of the OCAs (b) (4). The systemic exposures to the conjugates are several folds of the parent drug with similar pharmacological activity.

5.6 QTc Interval Assessment

No significant QTc prolongation effect of obeticholic acid (OCA 100 mg) was detected in the thorough QT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between obeticholic acid (OCA 100 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The selected suprathreshold dose, 100 mg once-daily for 5 days, is reasonable. OCA 100 mg for 5 days is considered the maximum tolerated dose. On Day 5, the predicted C_{max} ratios of total

OCA, OCA, glyco-OCA and tauro-OCA relative to the steady-state exposure after a 10-mg dose (therapeutic dose) are approximately 3.9, 7.2, 5.0 and 2.8. There are no indication of a relationship between QT interval and OCA concentrations. (Review by Huifang Chen , Quianyu Dang, October 21st, 2015)

5.7 Analytics

The concentrations of OCA, glyco-OCA, and tauro-OCA were determined in plasma and urine using a validated high performance liquid chromatography tandem mass spectrometry (LC/MS/MS) method. Four validated plasma and three validated urine LC/MS/MS methods were developed to characterize the pharmacokinetic properties of OCA and its conjugates. These were acceptable.

(b) (4)

(b) (4) All three labs did daily calibration and demonstrated that the equipment was operating in accordance with the equipment manufacturers' standards

The assay kits used for measuring ALP and total bilirubin in these labs are 510(k) approved. All three labs used methods based on the same general reactions for the two analytes. (b) (4)

The equipment/reagents used were commercially available from lab equipment manufacturers.

There are some minor differences in method details (b) (4) See the clinical pharmacology review for the details of the differences. Each of the three labs performed validation of the commercial tests to verify acceptable performance with focus on within run precision and total precision. The within run precision and total precision are reported to be < (b) (4)%. According the Sponsor, internal standard checks were performed daily using two QC sample levels.

Clinical Pharmacology Comment:

The accuracy in each lab was not adequately evaluated according to the current recommendations on commercial diagnostic kits in Draft Guidance on Bioanalytical Method Validation published in September 2013, however, the pivotal trial started before the release of this Guidance. The interpretations of the clinical results are not impacted by the incomplete accuracy data. The Sponsor performed efficacy analysis on primary endpoints using uncorrected lab values and concluded that efficacy remained the same.

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6. Clinical Microbiology

This formulation was an oral tablet and there are no outstanding microbiology issues.

7. Clinical/Statistical- Efficacy

Table 5: Clinical/Statistical Review Team

| Division | Reviewer |
|---|---------------------------|
| Division of Gastroenterology and Inborn Errors Products | |
| Medical Reviewer | Ruby Mehta, MD |
| Cross Discipline Team Leader | Lara Dimick-Santos, MD |
| Associate Director | Dragos Roman, MD |
| Office of New Drugs – ODE3 | |
| Deputy Director | Amy Egan, MD |
| Division of Biometrics 3 | |
| Mathematical Statistician | Benjamin Vail, MS |
| Mathematical Statistician | Min, PhD |
| Mathematical Statistician | Andrejus Parfionovas, PhD |
| Team Lead, Mathematical Statistician | Yeh-Fong Chen, PhD |
| Division Associate Director | Sue-Jane Wang, PhD |

Sections of this review were copied from the reviews of Benjamin Vail, mathematical statistician Min Min, PhD, mathematical statistician and Ruby Mehta, MD, medical reviewer and the Divisions Background package for the Advisory Committee meeting held April 7th, 2016.

The Applicant submitted a single phase 3 pivotal trial and 2 phase 2 controlled clinical trials as well as multiple phase 1 trials to support the application. This section will review the results of the two phase 2 trials briefly and the phase 3 trial in more depth. This section will also discuss the use of the surrogate biomarker and the Teams approach to the analysis of the “reasonable likelihood” of the change in ALP to predict clinical benefit in this population.

7.1 Discussion of use of Alkaline Phosphatase as a Potential Surrogate Endpoint

As noted previously in this review (Section 2.4 on page 9), during IND meetings the Applicant discussed the use of alkaline phosphatase alone as a surrogate endpoint for drug approval for their product for a PBC indication under that accelerated approval pathway. The Division did not agree that the Applicant had submitted adequate evidence or justification to support that ALP reduction alone was reasonably likely to predict clinical benefit. Therefore, the Applicant worked with an academic consortium that formed The Global PBC Study Group that performed 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., 2014⁸). The Applicant subsequently leveraged the results from this independent study to construct the composite endpoint used in the pivotal study (747-301) which was a combination of ALP and TB improvement.

The choice of specific cut-points for the phase 3 program (such as an $ALP \leq 1.67 \times ULN$) was also based on analyzing additional data generated by other investigators in the PBC field (Kumagi et al., 2010⁴) and on a final determination that the “Toronto II” criteria (i.e., $ALP \leq 1.67 \times ULN$ and $TB \leq ULN$) 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 shows 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 the pivotal 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 majority of patients (93%) enrolled in trial 747-301 only had ALP elevations with normal TB, a finding consistent with early stage PBC. In addition, the vast majority of patients (92%) 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 program) could not be necessarily applied to the trial 747-301 patient population without further scrutiny.

⁸ 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

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 was 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, The Division approached the Global PBC study group via the Applicant and requested the data from the study. With some delay secondary for the need to obtain consent for the data to be released to the FDA, the data from the study was released to the FDA. It was sent to a DMF file in the FDA and the Applicant did not have access to these data sets, but could see any analysis per the agreement with The Global PBC Study Group. Obtaining this data resulted in a major amendment and moving the PUDFA date back 3 months to allow analysis to be performed. The statistical team subsequently 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 (See below).

Discussion of ALP Variability

The variability of the assay method to determine ALP and the correction factors employed by the 3 different clinical laboratories used in the phase 3 clinical trial was assessed by the clinical pharmacology reviewer, Elizabeth Shang, PhD, and found to overall be less than 10%.

The baseline day to day variability in ALP in patients with PBC is not addressed in the literature and was not known. The review team requested analysis of the phase 2 and 3 clinical trials to analyze variability around the baseline in both the placebo groups and treatment groups. The baseline variability had a mean standard deviation (SD) of approximately 20 U/L. For a patient entering the trial with an ALP of 300 U/L a 15% change would be 45 U/L. The review team concluded that while there was significant variability in the ALP levels in patients it did not affect the results of the analysis in that the results remained robust across all cut-points analyzed.

7.2 Global PBC Study Group Analysis

CDTL Comment:

The Global PBC study group data was analyzed to see if it could support the surrogate endpoint of reduction in ALP being reasonably likely to predict clinical benefit. The team reasoned that if the reduction in ALP predicted clinical benefit in patients treated with UDCA in the Global PBC data sets then it was supportive of accepting that the reduction in ALP would be reasonably likely to predict clinical benefit in PBC patients treated with OCA. The team recognized that the two drugs had different mechanisms of action; however the mechanism of action of OCA was theoretically plausible and would reasonably be expected to affect the causal pathway

of PBC progression and ALP levels. Therefore, supporting the acceptance of ALP reduction alone as a surrogate “reasonably likely to predict”, with the analysis of the Global study data was essential to this application.

Extracted from the review of Min Min, PhD., and the background summary package for the Advisory Committee Meeting

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 patient's 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 1.67 x ULN,

patients whose baseline ALPs (as a multiple of ULN) are between 1.67 and any other derived ALP value (i.e., $> 1.67 \times \text{ULN}$) can only be responders if including the additional percent reduction criterion. In other words, any other absolute derived ALP value ($> 1.67 \times \text{ULN}$) 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 in Dr Min's review, the combination of $2.0 \times \text{ULN}$ and either 15% or 40% reduction performed better than $1.67 \times \text{ULN}$ and 15% reduction, we propose the following stratified cutoff to take into account the aforementioned patients in our cutoff selections:

- (1) ALP less than $1.67 \times \text{ULN}$ at Month 12 and at least 15% decrease from baseline for the patients whose baseline ALP were between 1.67 and $2.0 \times \text{ULN}$; **or**
- (2) ALP less than $2.0 \times \text{ULN}$ at Month 12 and at least 40% decrease from baseline for the patients whose baseline ALP were at least $2.0 \times \text{ULN}$)

From the above definition, our proposed stratified cutoff resulted in similar point estimates of C-statistic compared to other combined cutoffs of (a) $2.0 \times \text{ULN}$ and 15%, (b) $2.0 \times \text{ULN}$ and 40%, (c) $1.67 + 2.0 \times \text{ULN}$ and 15%, (d) $1.67 + 2.0 \times \text{ULN}$ and 40% (i.e., 0.68 to 0.69 in the training sets and 0.68 to 0.70 in the testing sets, respectively). We examined the robustness of our proposed stratified cutoff's predictability of transplant-free survival in comparison with protocol defined cutoff (i.e., $\text{ALP} < 1.67 \times \text{ULN}$ 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.

CDTL Comment:

See the review of Min Min, PhD., for the full details of the review, however the statistical analyses did support that ALP reduction alone as analyzed by the best fit primary endpoint (and several other endpoints) did have a reasonable like hood of predicting clinical outcomes of death and transplant in patient with PBC treated with UDCA, which supported its acceptance as a surrogate in this application.

7.3 Phase 2 Trial 747-201 Monotherapy and Dose Ranging

See clinical review by Dr. Ruby Mehta.

Study 747-201 is a double-blind, placebo controlled, multicenter (18 centers in 6 countries) trial, enrolling 60 early disease PBC patients (93%) as defined by Rotterdam criteria, out of which 59 patients were randomized 1:1:1 in parallel arm to study OCA 10 mg, OCA 50 mg OCA, and placebo and administered for 12 weeks (85 days). The study was completed by 48 patients and PK data is available for 34 patients. Of the 59 patients enrolled, 93% patients had elevated ALP; 81% patients had positive AMA titers.

Primary efficacy endpoint:

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

The planned sample size was approximately 120 patients (40 patients in each of the 3 treatment groups). However, due to difficulties with patient recruitment into the study, the final enrollment was approximately 20 patients per group. Overall, a sample size of 20 patients per group resulted in 49% power to detect an effect size of 0.6466 for the difference in the primary efficacy endpoint.

The 45% of patients enrolled in the OCA 10 mg arm had moderately advanced disease stage in comparison to 6% enrolled to OCA 50 mg and 13% in placebo treatment arm. The rates of patient discontinuation were almost 50% in patients dosed with OCA 50 mg. Mean ALP values were higher in trial 747-201 than those in the pivotal trial (747-301), mean ALP was 431 and ALP in concentration in ULN was 3.7 x ULN. Mean Conjugated bilirubin was in normal reference range in majority of patients.

Primary efficacy endpoint

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

The effect of OCA treatment on serum ALP levels were seen at week 2 and the response was durable for the entire duration of the trial. There was no apparent difference in the magnitude of improvement between the 2 OCA doses. GGT was also noted to decrease, and mild improvements in AST, ALT and bilirubin were seen. Other markers of inflammation also improved.

**Table 6: Percent Change in ALP Levels (U/L) from baseline to EOS:
 ITT Population (N = 59) Trial 747-201**

| 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 |

| | | | |
|-----|----|---------|---------|
| a b | NA | <0.0001 | <0.0001 |
|-----|----|---------|---------|

Safety - Phase 2 Trial 747-201

No deaths were reported during the conduct of the trial. Only a single SAE of rash was reported over the course of the study and occurred in a placebo treated patient.

All placebo patients (n = 23) completed the study

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

In the OCA 50 mg arm, of 6 (38%) out of patients 16 discontinued due to pruritus

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

Adverse event related to gastrointestinal disorders was higher in patients who received OCA 50 mg compared with placebo, with the exception of nausea.

No serious adverse event in the SOC “Hepatobiliary Disorders” occurred in this study. One event that occurred in the OCA 10 mg arm was a patient who experienced a TEAE of hepatic pain that was mild in intensity.

Mean LDLc was increased and HDLc were reduced in patients treated with OCA and not in patients who were in the placebo arm. At Day 85/ET, mean changes from Baseline in HDLc were -0.33 (0.50) mmol and -0.44 (0.48) mmol in the OCA 10 mg and OCA 50 mg arms, respectively, and -0.04 (0.21) mmol in the placebo arm. There were patients who had HDLc reductions as low as 20 mg/dL as well as reduction > 1 SD (>22 mg/dL) change in 85 days. Patients who discontinued from trail also affected the interpretation of final HDLc reductions.

Conclusions:

OCA appeared to have efficacy as monotherapy in PBC patients in decreasing ALP in this small underpowered trial. There was no dose response increase in efficacy between the 10 mg and 50 mg dose. Pruritus was the most common adverse reaction and was more severe, leading to more discontinuations in the 50 mg dose. Mean HDLc levels were reduced mildly; however some patients had significant reductions.

7.4 Phase 2 Trial 747-202 Dose Ranging - in Combination with UDCA

This is a 3 month multi-center, randomized, double-blind, placebo-controlled, multi-dose, parallel-arm trial to investigate the efficacy and safety of OCA 10 mg, 25 mg, and 50 mg doses, as compared with placebo in patients with PBC in combination with UDCA.

This trial was conducted in 8 countries at 30 investigational sites, with 30 investigators. This included 11 Investigators (11 sites) in the United States (US), 6 Investigators (6 sites) in Canada, 4 Investigators (4 sites) in Germany, 4 Investigators (4 sites) in the United Kingdom (UK), 2 Investigators (2 sites) in The Netherlands, 1 Investigator (1 site) in Austria, 1 Investigator (1 site) in France, and 1 Investigator (1 site) in Spain. The trial was started on 30th October 2007 and completed on 8th Sept 2009.

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

1. Alkaline phosphatase (ALP) levels
2. Safety

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

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

A total of 222 adult patients were screened, of which 165 patients met the study entry criteria and were randomized as follows: 38 patients to placebo arm; 38 patients to OCA 10 mg arm, 48 patients to OCA 25 mg arm, and 41 patients to OCA 50 mg.

Key inclusion criteria were:

1. Proven or likely PBC, as demonstrated by the patient presenting with at least 2 of the following 3 diagnostic factors:
 - a. History of increased ALP levels for at least 6 months prior to Day 0
 - b. Positive antimitochondrial antibody (AMA) titer
 - c. Liver biopsy consistent with PBC
2. on a stable dose of UDCA for 6 months

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3. ALP between 1.5 and 10 x ULN
4. Direct bilirubin \leq 2 x ULN, ALT or AST \leq 5 X ULN; serum creatinine \leq 1.5 mg/dL (133 μ mol/L)
5. Exclusion of patient with sever pruritus

Primary Efficacy endpoint:

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

The data quality provided by the Applicant was acceptable to the reviewers.

Trial Results Phase 2 747-202

A total of 136 (82%) patients completed the study. Of the 29 (18%) patients who did not complete the study. Early discontinuations were primarily due to AE of pruritus. The second most common reason for not completing the study included protocol mandated discontinuation criteria of elevated conjugated (direct) bilirubin (2 patients in OCA 50 mg arm, and 1 patient in OCA 10 mg arm or elevated AST/ALT levels (1 patient in OCA 50 mg arm). Finally, 2 other discontinuations included withdrawal of consent (1 patient) and lost to follow-up (1 patient). There was a high dropout rate in the OCA 50 mg dose treatment arm. A total of 61% of patients on OCA 50 mg completed the trial for the duration of 3 months compared with 97% completion patients in the placebo arm completed the trial.

Table 7: Analysis Populations Trial 747-202

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

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

The majority (95%) of the trial patients in early stage disease category as per Rotterdam criteria, i.e., total bilirubin and albumin at baseline were both within the normal range. There are slightly less numbers of patients in placebo arm with moderately advanced stage disease in comparison to OCA treatment arms. The mean baseline ALP values were 2.4x to 2.5x ULN. Baseline ALP values were similar across all treatment arms. The total bilirubin data is not shown here, however, TB was normal in the majority of patients, with abnormal baseline TB levels observed in 20 patients out of 165 enrolled patients. There were 3 patients with conjugated (direct) bilirubin levels >2x ULN who were included in the study.

There were several protocol violations/deviations; however the protocol deviations were determined not to have interfered with efficacy or safety assessments.

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

Efficacy Results - Primary Endpoint

The ALP mean percent reduction was seen at all OCA doses, relative to placebo and the mean percent reduction was generally similar across all OCA dose arms and was statistically significant compared to placebo. Doses higher than 10 mg do not provide further ALP reduction.

Table 8: Percent Change in Serum ALP Levels (U/L) from Baseline to EOS: mITT Population (N = 161) Trial 747-202

| 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 | NA | <0.0001 | <0.0001 | <0.0001 |
|---------|----|---------|---------|---------|

Table source: CSR 747-202 page 76 of 1652

A 40% reduction in ALP is seen in 0%, 21%, 15% and 26% of patients in the placebo, OCA 10 mg, 25 mg and 50 mg arms respectively. These results highlight that the dose exposure response seems to a plateau at 10 mg dose.

A post-hoc analysis was performed to determine the percentage of patients achieving the primary endpoint of the phase 3 study 747-301 (ALP <1.67x ULN and bilirubin ≤ULN and ALP ≥15% reduction). In this post-hoc analyses approximately 40% patients in OCA-treated patients achieved the composite endpoint at Day 85/EOS compared to 9% of the placebo-treated patients.

There were minimal changes in AST/ALT and TB during the trial. There were some improvements in other markers of liver disease and inflammation that support the primary efficacy outcome.

There were no significant differences in subgroup analyses of the ALP response, however too few patients greater than 65 years of age and male patients (8) were enrolled to permit statistical analysis for these groups.

Safety Trial 747-202

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

More patients in the OCA 50 mg group experienced moderate to severe TEAEs compared with other treatment groups. The incidence of severe TEAEs were dose-related, and were reported by 16%, 21%, 44%, and 8% of the patients in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo groups, respectively.

Overall, 7 patients (4%) experienced an SAE in the study. The incidences of SAEs reported in the study were as follows: 1 patient (3%) in the placebo arm had an SAE of dyspnea, 1 patient (2%) in the OCA 25 mg arm had an SAE of salivary gland neoplasm, 2 patients in the OCA 50 mg arm experienced angina pectoris and angioedema, and 3 patients in the 50 mg arm experienced GI hemorrhage, jaundice, and primary biliary cirrhosis (PBC flare). There were no deaths.

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

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

Pruritus

The severity of pruritus is dose-related. The overall incidence of TEAEs of pruritus was higher in the OCA 25 mg and OCA 50 mg treatment arms compared with the OCA 10 mg and placebo arms (47%, 85%, 80%, and 50% of patients in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo arms, respectively). The incidence of the TEAE of pruritus in the OCA 10 mg arm was similar to that in the placebo arm. The median times to the first episode of pruritus were 6.5 days, 5 days, 2 days, and 25.0 days in the OCA 10 mg, OCA 25 mg, OCA 50 mg, and placebo arms, respectively.

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

Although the overall incidence of pruritus was similar in placebo arm and OCA 10 mg treatment arm, there was a higher incidence of pruritus interventions were required in patients dosed with OCA 10 mg (67%) in comparison placebo (47%) treatment arm. Additionally, 100% patients in placebo treatment arm responded to treatment interventions, with none requiring treatment interruption or discontinuations in comparison to patients on OCA treatment arms. The pruritus was reversible with drug discontinuation. The resolution of pruritus was faster in OCA 10 mg arm in comparison to OCA 50 mg arm.

Hepatic related adverse events

One patient (3%) in the OCA 10 mg arm experienced a hepatic-related TEAE compared to 4 patients (8%) in the OCA 25 mg and 9 patients (22%) in the OCA 50 mg arms who experienced a hepatic-related TEAE. No patient in the placebo arm experienced a

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hepatic-related TEAE. Most biochemical changes (ALT/AST and TB) increase was seen in early stage disease patients. Only one patient with moderately advanced disease had elevation of ALT/AST and TB.

Lipid-Related Adverse Events

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

A 10 to 17 point reduction in mean HDLc was noted in the OCA 10 mg, 25 mg and 50 mg arms compared with a smaller but positive change in HDL within the placebo arm.

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

Four patients treated with OCA had cardiovascular events; however no conclusion could be made based on these small numbers of events.

Conclusions

This trial showed again that OCA was effective at reducing ALP in patients with PBC. Again the 10 mg dose was as effective as the 25 and 50 mg doses; however there was an increase in adverse events, esp. pruritus in the higher doses. There were also increased incidence of liver related adverse events and elevations in liver biochemistries mostly with the doses greater than 10mg. Decreases in HDLc which were significant in some patients were again seen.

7.5 Pivotal Study Design Trail 747-301

The lone pivotal trial used for the basis of this accelerated approval is study 747-301 which is a phase 3, 12-month, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study. This study utilized the composite endpoint:

The double-blind/placebo-controlled portion of this trial has already been locked and unblinded. Patients completing this study had the option of additional long term open-label extension up to five years; this open-label rollover period is still currently ongoing. A total of 180 patients were targeted for enrollment, and 217 patients were ultimately recruited (with 216 actually being dosed) to

participate in this study. There were two short term phase 2 studies (i.e., 747-201 and 747-202), but these studies enrolled a very small set of patients using the proposed indicated dose.

This study was designed as a multinational (with a total of 13 participating countries within 3 geographic regions), multicenter (with a total of 59 participating study sites), randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of OCA in patients with PBC. The original 747-301 trial protocol was finalized on September 6, 2011, and the trial was subsequently started on March 19, 2012. The completion date of the 12-month double-blind portion of the study was on December 18, 2013; the long term open-label extension period is still currently ongoing. Three amendments (i.e., on January 18, 2012, April 4, 2012, and September 24, 2012) were made to the original protocol as pertaining to the double-blind portion of the study. Each amendment was minor and/or administrative in nature without changing key pre-specified features of the original protocol. This written review reflects the final version (i.e., dated September 24, 2012) of the double-blind portion of the protocol.

The submitted data quality for this study appeared to be adequate. There were no ‘Official Action Indicated’ (OAI) issues from site inspections conducted by the Office of Scientific Investigations (OSI); any issue was deemed as either ‘No Action Indicated’ (NAI) or ‘Voluntary Action Indicated’ (VAI). As per OSI, the 747-301 study appeared to have been conducted adequately, and the data generated by the study appeared acceptable in support of the respective indication.

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

- Have at least one (i.e., “and/or”) of the following qualifying biochemistry values
 - $ALP \geq 1.67 \times \text{Upper Limit of Normal (ULN)}$
 - $TB > ULN$ but $< 2.0 \times ULN$
- Taking UDCA for at least 12 months (with a stable dose for at least 3 months) prior to study start, or unable to tolerate UDCA (i.e., no UDCA usage for at least 3 months) prior to study start.

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

- Pre-treatment ALP $> 3.0 \times \text{ULN}$ and/or aspartate aminotransferase (AST) $> 2.0 \times \text{ULN}$ and/or TB $> \text{ULN}$; ('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).

Patients were then randomized in a 1:1:1 ratio to receive 10 mg OCA, 5 mg OCA with the option to titrate up to 10 mg at Month 6 (i.e., the 'OCA Titration' treatment arm), or matching placebo.

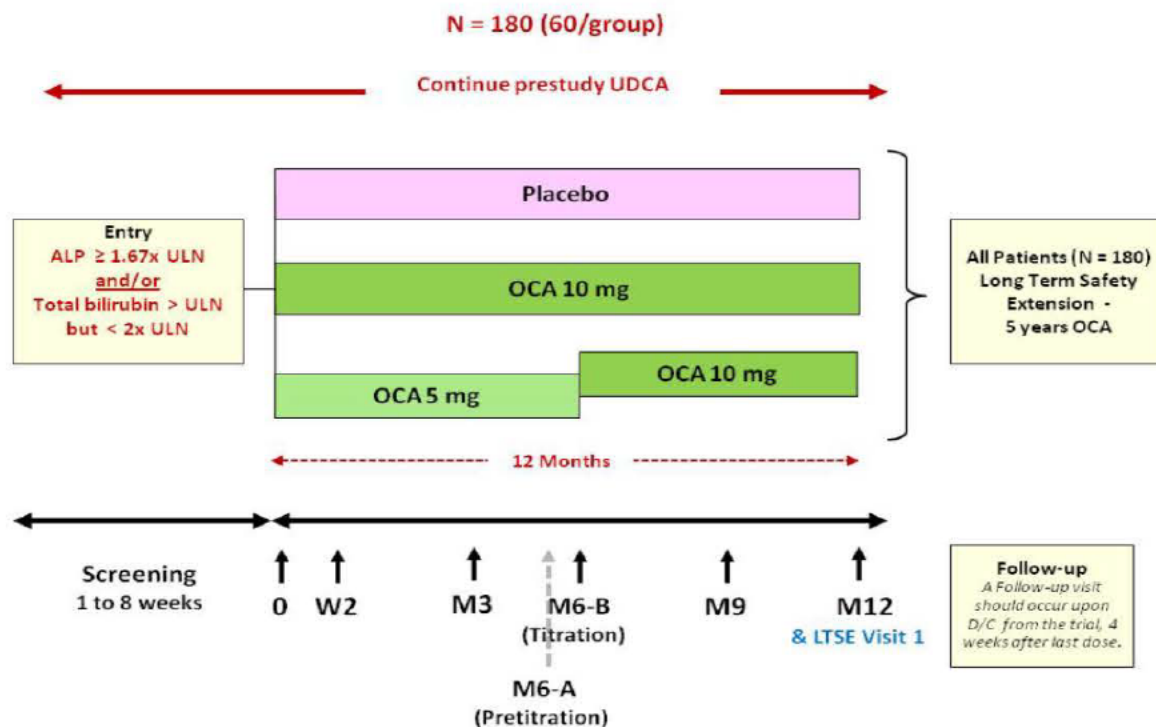
For all treatment arms (although specifically targeting the blinded OCA Titration treatment arm), the criteria to be eligible for up-titration at the 6 month time point/visit, assessed by the on-site investigator (and subsequently made via the IVRS/IWRS), was if the patient met any (i.e., "and/or") of the following conditions:

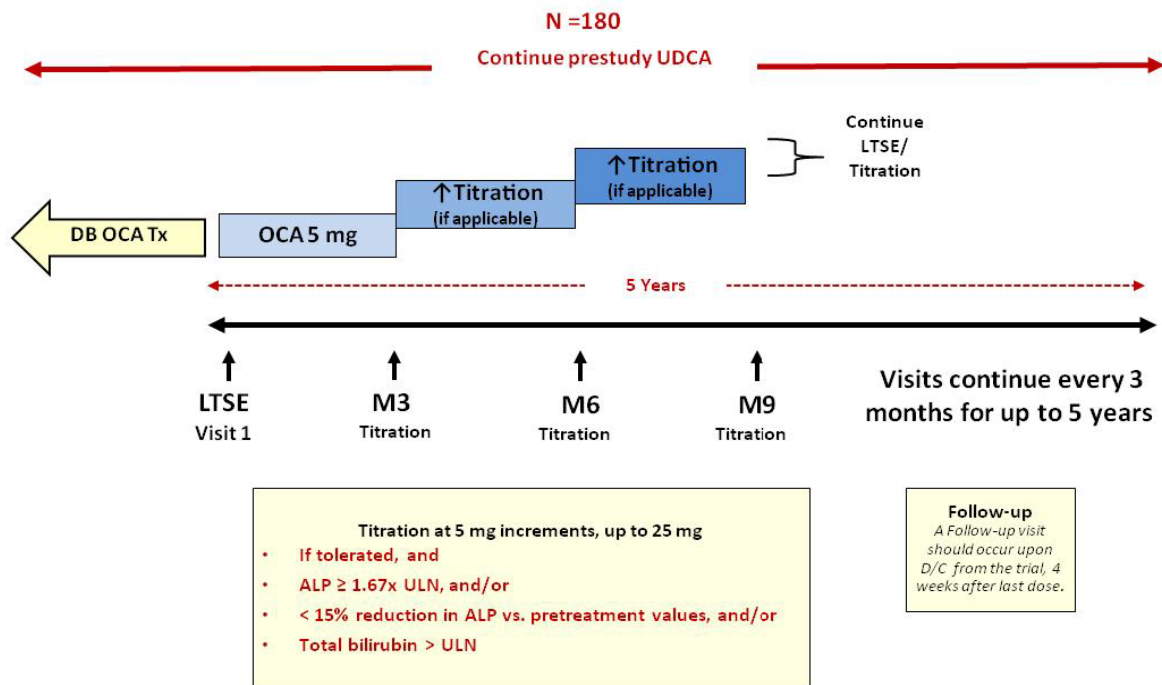
- ALP $\geq 1.67 \times \text{ULN}$
- TB $> \text{ULN}$
- $< 15\%$ ALP reduction at Month 6 versus the mean double-blind pre-treatment ALP value(s)
- Provided adverse events (AEs) (e.g., severe pruritus) did not limit the administration of a higher dose.

The overall study scheme for both the double-blind and LTSE periods are shown in Figure 2 below. Note that the target sample size for the study was for 180 patients (i.e., 60 per treatment arm); a total of 217 patients were ultimately enrolled and randomized with 216 being administered at least one dose of study drug.

Throughout the execution of this protocol, an IDMC operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there were no formally planned interim analyses for this study.

Figure 2: Schematic Diagram of Double-Blind Treatment and LTSE Periods





Source: Figures 1 and 2 from pgs. 31-32 of the 747-301 protocol.

Note: The August 25, 2014 protocol amendment capped the maximum total dose at 10 mg for the LTSE period.

In accordance with the study's lone primary objective, as stated above, the following primary endpoint (which was a composite endpoint) was pre-specified within the original protocol.

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 $< 1.67 \times ULN$
- 12-Month value of TB $\leq ULN$ (i.e., within normal limits)
- ALP reduction from baseline at Month 12 $\geq 15\%$.

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. 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). 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.

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. 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.

Handling of Dropouts/Missing Data

To 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 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. The final results and conclusions were not influenced by the limited missing data encountered in the study.

Other Issues – ALP endpoint

See Section 7.7 on page 44. The statistical reviewer, Benjamin Vali, analyzed the trial data (analyzing trial patients who were exclusively early stage PBC patients, who also had screening/baseline $ALP \geq 1.67 \times ULN$ while being administered UDCA) utilizing the newly determined endpoint criterion as developed by Min Min, PhD and the statistical team. Other relevant ALP cut points explored by Dr. Min in her review were also applied to this subset of trial patients for sensitivity analysis purposes.

7.6 Study Results – Phase 3 Trial 747-301

Patient Disposition and Demographic and Baseline Characteristics

217 patients were enrolled and randomized into the 747-301 study with 216 being administered at least one dose of study drug (i.e., part of the ITT analysis set as defined above). The lone patient who was randomized but not dosed was from the OCA Titration treatment group; 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 (the patient who dropped out immediately after randomization withdrew consent). 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 at Month 6 remained on 5 mg OCA.

See Table 4 below for patient disposition.

Table 9: Disposition (ITT) – 747-301

| | 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%) |
| 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: FDA Statistical Reviewer's Table generated from the 747-301 ADSL dataset.

Note: Denominators for percentages are N.

See the statistical review by Benjamin Vali for a full description of demographic and baseline characteristic; however the demographic and baseline characteristics were balanced for all presented variables, between the randomized treatment groups.

Efficacy Results – Primary Endpoints

Table 10: Proportion of Patients who Achieved Response (ITT) Trial 747-301

| Statistics | 10 mg OCA (N = 73) | OCA Titration (N = 70) | Placebo (N = 73) |
|---|---|---|-------------------------|
| Response at Month 6 – n (%) [1] [2] Corresponding 95% Wald CI | 37 (50.7%) 39.2%, 62.2% | 24 (34.3%) 23.2%, 45.4% | 5 (6.9%) 1.1%, 12.6% |
| Response at Month 12 – n (%) [1] [2] Corresponding 95% Wald CI CMH Test p-value [3] Corresponding Breslow-Day Test p-value | 34 (46.6%) 36.5%, 59.4% <0.0001 0.9072 | 32 (45.7%) 34.0%, 57.4% <0.0001 0.5045 | 7 (9.6%) 2.8%, 16.3% |
| (1) ALP < 1.67×ULN at Month 12 – n (%) [2] | 40 (54.8%) | 33 (47.1%) | 12 (16.4%) |
| (2) TB ≤ 1.0×ULN at Month 12 – n (%) [2] | 60 (82.2%) | 62 (88.6%) | 57 (78.1%) |
| (3) Decrease in ALP ≥ 15% at Month 12 – n (%) [2] | 57 (78.1%) | 54 (77.1%) | 21 (28.8%) |

Source: FDA Statistical 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]: Patients with missing data at these timepoints were designated as non-responders.

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

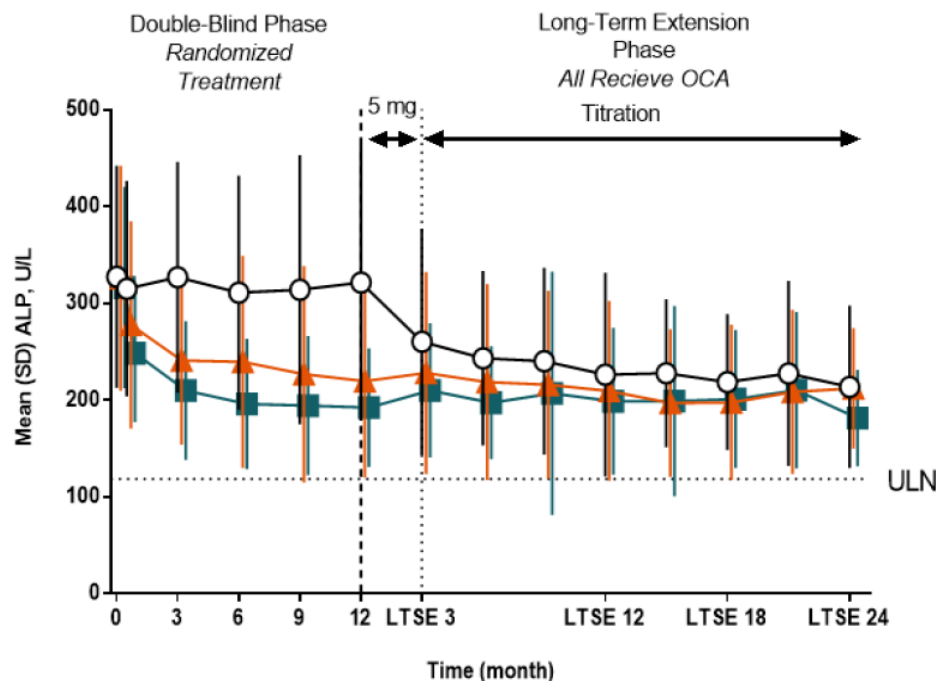
It can be observed from Table 10 above that both OCA treatment groups showed a superior difference in the proportion/percentage of patients achieving response at Month 12 when individually compared to placebo using the CMH test. The corresponding Breslow-Day test result shows that the treatment effects 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 statistical reviewer, 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 laboratory values (as presented) and original (i.e., uncorrected) laboratory values. All of the previously presented analyses were re-conducted utilizing a baseline value that was the median of all pre-first dose measurements, and, separately, a traditional baseline definition; there was no impact on study conclusions with either approach. Considering the Applicant's pre-specified step-down/closed sequential testing procedure, formal hypothesis testing is stopped at this point. Any subsequent inferential statistic reported below should be considered exploratory.

See the statistical review for analysis of ALP at month 12 and change from baseline in ALP which supported the conclusions of the primary endpoint.

After completing the 12-month double-blind treatment period, 193 out of the 216 ITT patients (i.e., 64 10 mg OCA, 63 OCA Titration, and 66 Placebo patients) continued on open-label OCA treatment during the LTSE period. Figure 3 below presents ALP concentration over time for all ITT patients, organized by originally randomized treatment group, through the currently ongoing open-label LTSE period up to the latest data cut made on June 29, 2015. It can again 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 remained stable during the LTSE period suggesting durability of response. It can also be seen that ALP levels for placebo patients were flat during the first 12 months; however, these levels started decreasing immediately, and ultimately remained stable, during the LTSE period once these patients started OCA administration.

Figure 3: ALP Concentration (U/L) from Randomization through Latest LTSE Data Cut – 1 (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 |

Other Analysis of Alkaline Phosphatase

ALP normalization was seen in 1 patient in OCA titration arm and 5 patients in OCA 10 mg arm and in zero patients in placebo arm. Additionally, only one patient in the placebo arm reached $\geq 40\%$ ALP reduction whereas 21 patients in the OCA titration arm and 25 patients in the OCA 10 mg arm achieved this reduction. This result is statistically significant.

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About 1/3 of patients had ALP >3 x ULN the Applicant analyzed the effect of OCA based on baseline ALP tertiles (lower tertile <250.5 U/L, middle tertile \geq 250.5 U/L to <339.6 U/L, and upper tertile \geq 339.6 U/L). Patients reaching primary endpoint are as follows:

| | | | |
|------------------------|------------------|----------------------------|-------------------|
| <u>Lower Tertile:</u> | 18% placebo arm, | 71% OCA titration arm, and | 65% OCA 10 mg arm |
| <u>Middle Tertile:</u> | 13% placebo arm, | 50% OCA titration arm, and | 50% OCA10 mg arm |
| <u>Upper Tertile:</u> | 0% placebo arm, | 17% OCA titration arm, | 19% OCA 10 mg arm |

Total Bilirubin

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. It should be additionally noted that of these 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 overall responders at Month 12 as pertaining to the pre-specified primary composite endpoint. It should also 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 Applicant's baseline definition was used for all presented calculations. See the statistical review for the details of the TB levels.

Other Exploratory Efficacy Endpoints:

GGT, ALT, and AST

Baseline GGT was elevated across all 3 treatment arms (approximately 9x ULN to 12x ULN) consistent with cholestasis. Mean transaminases (ALT and AST) were also elevated at baseline approximately 2x ULN. Improvements in GGT, ALT and AST were observed as early as 2 weeks, with the largest magnitude of response observed by month 3. Following month 3, the magnitude of response was sustained through month 12 for GGT values, while the response was more variable for ALT and AST values. These findings support the primary efficacy evaluation.

Albumin, Prothrombin Time, and INR:

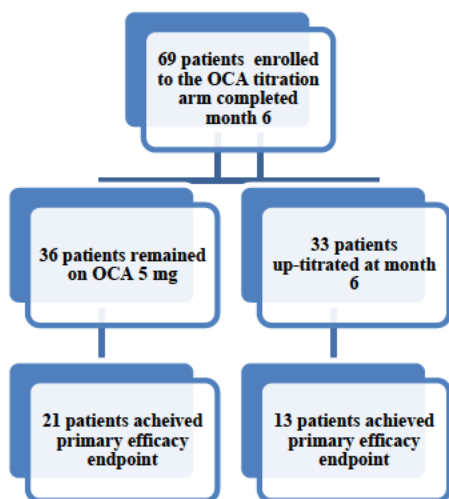
Baseline albumin, prothrombin time, and INR values were within normal ranges across all 3 treatment arms at baseline, during and after completion of the trial. No statistical differences between placebo and OCA treatment arms were observed; no worsening of these parameters was noted over the 12-month period across all 3 treatment arms.

Titration Arm Analysis

The patients in the titration arm were up-titrated in a blinded fashion, in that all patients were evaluated for potential up-titration and the investigators remained blinded to the treatment. The criteria for up titration were slightly different than the primary endpoint as they were:

- ALP $\geq 1.67 \times$ ULN or
 - ALP decreased by less than 15% from baseline or
 - TB above ULN
- No significant intolerability issues.

Figure 4: Outcomes in Titration Group ITT – 747-301



Source: Clinical Review – Ruby Mehta, MD

7.7 Analysis of Subset of Trial 747-301 Population with using endpoint derived from the statistical analysis of PBC study data.

The analysis of the endpoint derived by the FDA statistical team was performed using a subpopulation from the trail that excluded patients on monotherapy and patients with elevated TB such that the populations would match. This resulted in 181 patients from trial

747-301 being included in this analysis. See Table 9 in Benjamin Vali’s review for complete demographics and baseline characteristics. Vali noted in his review that there were areas of imbalance; however, given the non-concurrent nature of these cohorts, the data were reasonably balanced between the populations. 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 was gathered and reported in the Global PBC Study, or may represent a real difference.

As presented within Dr. Min’s review, many different cut-point criteria that utilized ALP reduction alone after 12 months of observation for reasonably 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.

Applying all of these explored ALP cut points at 12 months resulted in consistent relative differences in response rates between the treatment groups (i.e., similar relative differences in response rates between the treatment groups).

The stratified ALP cut point at Month 12 that was the best performing was defined as follows:

If baseline ALP was $\geq 2.0 \times \text{ULN}$, then a patient would be designated as a responder if both of the following conditions were met:

- 12-Month value of ALP $< 2.0 \times \text{ULN}$
- ALP reduction from baseline at Month 12 $\geq 40\%$;

Else if baseline ALP was $\geq 1.67 \times \text{ULN}$ but $< 2.0 \times \text{ULN}$, then a patient would be designated as a responder if both of the following conditions were met:

- 12-Month value of ALP $< 1.67 \times \text{ULN}$
- ALP reduction from baseline at Month 12 $\geq 15\%$.

Table 11: Proportion of Patients who Achieved Response using Stratified Cut Point (Comparable ITT) - 747-301

| 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% |

| Statistics | 10 mg OCA (N = 60) | OCA Titration (N = 60) | Placebo (N = 61) |
|--|-----------------------|---------------------------|---------------------|
| <i>Baseline ALP</i> $\geq 2.0 \times \text{ULN}$ – 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 $\geq 40\%$ at Month 6 – n (%) [2] | 10 (23.8%) | 13 (27.7%) | 0 |
| ALP < 2.0×ULN and Decrease $\geq 40\%$ at Month 6 – n (%) [2] | 9 (21.4%) | 11 (23.4%) | 0 |
| <i>Baseline ALP</i> $\geq 1.67 \times \text{ULN}$ 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 $\geq 15\%$ at Month 6 – n (%) [3] | 16 (88.9%) | 11 (84.6%) | 1 (6.7%) |
| ALP < 1.67×ULN and Decrease $\geq 15\%$ at Month 6 – n (%) [3] | 16 (88.9%) | 10 (76.9%) | 1 (6.7%) |
| Response at Month 12 – n (%) [1] | 26 (43.3%) | 23 (38.3%) | 3 (4.9%) |
| Corresponding 95% Wald CI | 30.8%, 55.9% | 26.0%, 50.6% | 0.0%, 10.3% |
| <i>Baseline ALP</i> $\geq 2.0 \times \text{ULN}$ – 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 $\geq 40\%$ at Month 12 – n (%) [2] | 13 (31.0%) | 16 (34.0%) | 1 (2.2%) |
| ALP < 2.0×ULN and Decrease $\geq 40\%$ at Month 12 – n (%) [2] | 12 (28.6%) | 13 (27.7%) | 1 (2.2%) |
| <i>Baseline ALP</i> $\geq 1.67 \times \text{ULN}$ 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 $\geq 15\%$ at Month 12 – n (%) [3] | 14 (77.8%) | 10 (76.9%) | 2 (13.3%) |
| ALP < 1.67×ULN and Decrease $\geq 15\%$ at Month 12 – n (%) [3] | 14 (77.8%) | 10 (76.9%) | 2 (13.3%) |

Source: FDA statistical Reviewer’s Table 11: generated from ADLIVER dataset.

Note: Denominators for percentages are N.

[1]: Response is defined by the Stratified ALP Cut Point.

[2]: The denominator for this calculation is the number of patients with Baseline ALP $\geq 2.0 \times \text{ULN}$.

[3]: The denominator for this calculation is the number of patients with Baseline ALP $\geq 1.67 \times \text{ULN}$ but < 2.0×ULN.

It can be observed from Table 11 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 statistical reviewer 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; there was no impact on the results with either approach.

After completing the 12-month double-blind treatment period, 163 out of these 181 comparable ITT patients (i.e., 54 10 mg OCA, 53 OCA Titration, and 56 Placebo patients) continued on open-label OCA treatment during the LTSE period. ALP concentration over time for the 181 comparable ITT patients (organized by originally randomized treatment group, through the currently ongoing open-label LTSE period up to the latest data cut made on June 29, 2015), are reduced by both OCA treatment groups during the first 12 months, most notably during the first three months. These reduced levels remained stable during the LTSE period suggesting durability of response. ALP levels for placebo patients were flat during the first 12 months; however, these levels started decreasing immediately, and ultimately stabilized at a lower level, during the LTSE period once these patients started OCA administration.

Reductions from baseline in TB were only marginally greater in both OCA treatment groups relative to the placebo group. It can also be seen that TB levels for placebo patients slightly increased during the first 12 months; however, these levels started decreasing immediately, and ultimately remained stable, during the LTSE period once these patients started OCA administration.

As a whole in this trial, the changes in TB levels were observed to be small with treated patients TB remaining unchanged and a slight worsening of TB in the overall placebo group; however that may be attributable to outliers. No conclusion could be made from the small changes in TB seen in the clinical trial.

CDTL Comment:

In hepatobiliary liver disease transaminases (AST/ALT) are elevated indicating injury to liver cells. In cholestatic liver diseases, like PBC, ALP is elevated early in the disease indicating injury to bile ducts. In both diseases as fibrosis increases and there is loss of hepatic function TB begins to rise. Therefore, TB is a better marker of prognosis in later stages of disease when it is elevated and at some point ALP may return to normal and not be predictive of outcomes. TB may also be a useful surrogate in later stages of disease and additional analysis of the PBC global study group data should be performed to clearly identify what endpoint(s) could be candidate be used in patients with later stages of PBC, i.e., TB alone or a combination of TB and ALP and to which subpopulations of PBC patients each of these endpoints might apply.

Subgroup Analysis

The overwhelming majority of study participants were female (i.e., 90.7%) and white (i.e., 94.0%); hence, this precluded any meaningful/informative subgroup analysis for gender and race.

It appeared that more patients who were less than 65 years of age achieved a response in all treatment groups (i.e., 10 mg OCA, OCA Titration, and Placebo) relative to those that were greater than or equal to 65 years of age (i.e., the geriatric age group). However, since only 18.5% of all ITT patients were in the geriatric age group, these findings may not be reliable. Regarding the two different geographical regions, the results appeared consistent; additionally, these results were consistent with the overall ITT population

7.8 Monotherapy

The overwhelming majority of study participants were using UDCA (i.e., 92.6%).

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. Data from the long-term extension trial show 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. 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.

In an analysis of a pooled dataset consisting of the phase 2 (747-201) (including only patients with a baseline ALP > 1.67 x ULN) and phase 3 (747-301) 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 12: 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 = 27) | 1 (4) |

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| | |
|------------------------------|---------|
| OCA 10 mg (N = 24) | 9 (38)* |
| Combination (+ UDCA) | |
| Placebo (N = 106) | 5 (5) |
| OCA 10 mg (N = 105) | 43 (41) |

Source: FDA analysis

*The mean (95% CI) reduction in ALP in OCALIVA-treated patients was 246 (165, 327) U/L compared to an increase of 17 (-7, 42) U/L in the placebo-treated patients

Integrated Assessment of Effectiveness

Secondary to the fact that only one pivotal trial was submitted no integrated assessment of effectiveness was performed except for the above assessment of monotherapy.

7.9 Conclusions on the Substantial Evidence of Effectiveness

See the review of Benjamin Vail, mathematical statistician:

Overall, the design of the 747-301 pivotal study was deemed adequate from a statistical perspective, and the applicant’s corresponding SAP was deemed appropriate by the review team. There were no statistical review issues identified for trial that would preclude product approval. Although it was a single study the results were persuasive and consistent across sites and the additional phase 2 trials data supported the phase 3 trial results.

Although the design, statistical analyses and results of the pivotal trial appeared to be convincing and robust, the fundamental issue of the NDA overall, was that the patients enrolled in this phase 3 study were not adequately comparable to the broad spectrum of PBC disease patients studied by the Global PBC Group. This rendered, as questionable, the overall adequacy/applicability of the pivotal trial’s primary composite endpoint, which was to be used by the applicant as a basis for accelerated approval of this NDA. In particular, the primary composite endpoint was constructed based on the overall Global PBC study results and accordingly incorporated 12 month changes/reductions in both ALP and TB levels assuming elevated levels for each parameter. However, the enrolled trial patients primarily represented the early stage PBC disease population (whose patient’s only exhibit only elevated ALP levels as specified by the Rotterdam PBC disease staging criteria) who were also concomitantly using UDCA. Therefore the review hinged on the acceptability of ALP reduction alone as a surrogate reasonably likely to predict clinical benefit. One major factor that could support the ALP endpoint was data from the Global PBC study group that could analyze a group of patients with similar disease characteristics to see if the endpoint of reduction of ALP to less than 1.67 x ULN and at least by 15% was predictive of clinical benefit (death or transplant) in patients taking UDCA.

Dr. Min, an independent FDA statistical reviewer, who was intentionally asked not to study any 747-301 trial data, conducted her review using the submitted subject-level Global PBC Study data to adequately match a clinically meaningful subset of Global PBC Study patients. She ultimately confirmed the predictability of ALP, and the statistical team proposed a stratified cut point to further confirm OCA's efficacy in the treatment of PBC trial patients. However, note that the sponsor's original prespecified endpoint was also appeared to acceptably predict clinical benefit. The review team ultimately decided with the totality of the evidence that ALP reduction per the prespecified endpoint was reasonably likely to predict clinical benefit in patients with PBC taking OCA.

The phase 3 pivotal trial results showed a significant difference in the number of responders at 12 months, pertaining to the applicant's pre-specified primary composite endpoint, between both OCA treatment groups and placebo. The trial results also showed that OCA substantially reduced ALP levels, relative to placebo, after 12 months. The currently ongoing open-label, long-term, safety extension period suggests a sustained/durable OCA efficacy profile with respect to ALP levels. As a whole in this trial, the changes in TB levels were observed to be small, and TB levels were generally stable throughout OCA treatment exposure. This may very well have been attributed to the enrolled trial population primarily consisting of early stage PBC patients who were being administered UDCA; these patients are understood to exhibit reasonably low and stable TB levels over time. Consequently, this may render, as questionable, any potential claim that OCA therapy maintains low and stable TB levels within this studied patient population (i.e., early stage PBC patients using UDCA) because these TB levels most likely would have stayed low and stable regardless of OCA intervention.

If ALP reduction does predict clinical benefit in patients with PBC this application meets the substantial evidence of effectiveness criteria for approval.

See risk/benefit summary for a discussion of the approval based on ALP as a surrogate.

In Conclusion, I would support the approval of OCA for PBC based on the totality of the trial data and that ALP reduction appears to be reasonably likelihood to predict clinical benefit for this population with a serious and life-threatening disease and an unmet medical need.

8 Safety

8.1 Phase 2 Trial 747-203 - Evaluate Lipid Metabolism in PBC Patients

This was an open-label trial to evaluate effects of OCA 10 mg on lipoprotein, enrolling 26 patients with PBC for 8 weeks. UDCA use was allowed. Change in diet or exercise was not allowed during the trial. Patients with presence or history of clinically significant cardiac arrhythmias were excluded.

Concomitant medications that could affect cholesterol metabolism were prohibited as well as bile acid sequestrants.

Results

HDL cholesterol: A statistically significant decrease in the HDL cholesterol was observed at Week 4 and this effect was sustained, at approximately the same magnitude, through to the end of the treatment period at Week 8.

Mean LDL cholesterol concentration increased significantly from baseline following treatment with OCA at Week 4 and was sustained at Week 8. Following withdrawal of investigational product, LDL cholesterol concentration remained increased from baseline but a significant decrease was noted from Week 8 to Week 12.

CDTL Comment:

The Applicant states the small particle LDLc increased where as IDL and Large LDL particle did not increase. However, the clinical significance of these isolated small particle LDLc needs to be correlated with clinical outcomes.

No other new significant findings were noted in this trial.

8.2 Phase 3 Clinical Trial 747-301

In the phase 3 clinical trial a total of 216 PBC patients were enrolled, and were randomized as follows:

- 73 patients received placebo,
- 73 patients received OCA 10 mg for the total duration of the trial and
- 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.

One death occurred in the phase 3 clinical trial in an 82 yo male secondary to cardiac failure. 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.

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.

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.

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. The incidence of “severe pruritus” was 7% in placebo, 19% in OCA titration arm and 23% in OCA 10 mg arm.

Pruritus was evaluated by three tools; the itch domain of the PBC 40, which assesses impact of itching, the 5-D Pruritus Scale, total score assesses severity and impact of itching and the Pruritus Visual Analog Scale (VAS). These instruments were not intended to support efficacy or comparative safety claims in labeling; however the Clinical Outcomes Assessment (COA) Team was consulted to review the instruments (Selena Daniels, Pharm.D, MS, March 16th, 2016). The review criteria were not the same as would be required for an efficacy claim. This review concludes that these instruments appear fit-for purpose for this drug development program. However, it was unclear what threshold of change represents clinically meaningful deterioration on each of these scales.

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.

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.

CDTL Comment:

Pruritus is common in patient with PBC, though it tends to improve with onset of more advanced liver disease. It is apparently that there is a dose response increase in pruritus with OCA. Doses of 5 and 10 mg appeared to be fairly well tolerated and most patients can remain on treatment with use of bile acid sequestrants, antipruritic drugs or dose modification. It appears from the phase 3 clinical data that there is less pruritus in the titration group, therefore we agree with the Applicants proposal to start all patients at 5 mg and titrate the dose to 10 mg based on biochemical response and tolerability.

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.

CDTL 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. 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.

Lipid-Related Effect

HDLc levels at the OCA 10-mg and OCA 5-mg doses were reduced with both OCA doses and this reduction was sustained at month 12 (See Table 13).The LDLc increased by 1% in placebo, 6% in OCA titration and 6% in OCA 10 mg arm seen at week two.

Table 13: HDLc mean percent change (ITT) - Trial 747-301

| HDLc (mean percent change) | Placebo | OCA titration arm | OCA 10 mg arm |
|----------------------------|---------|-------------------|---------------|
| | | | |

| | | | |
|----------|----|-----|-----|
| Week 2 | 1% | 9% | 20% |
| Month 12 | 3% | 12% | 19% |

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).

No patients in the placebo arm, 4 in the titration arm and 5 in the OCA 10 mg arm had reductions in HDLc \geq to 2 standard deviations (SD) (i.e., 44 mg/ dL). One patient in placebo arm; 14 patients in OCA titration arm and 16 patients in OCA 10 mg arm had HDLc reduction >1 SD but <2 SD that is between 22-44 mg/dL. A few patients had significant reductions in HDLc.

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.

CDTL Comment:

While the mean changes in HDLc were not severe, in some patients significant decreases in HDLc were seen. With our current knowledge of lipid metabolism this change definitely had a potential to increase cardiovascular risk. The sponsor will continue to monitor for cardiovascular events in the confirmatory trial and the long-term safety trials. Patients HDLc and LDLc should be monitored a few months after starting treatment and periodically thereafter.

8.3 Integrated Summary of Safety

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 and 432 patients with PBC have been exposed to OCA, with dosing out to more than 4 years in 16 patients.

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.

8.4 Hepatic Adverse Reactions

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. Three patients had hepatic adverse events, (acute cholecystitis [25mg], hyperbilirubinemia [10mg], hypertransaminasemia [10mg]). All three of these events resolved with drug discontinuation.

Hepatic Events in PBC patients

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.

A total of 14 OCA-treated patients had 25 TEAEs that were classified within the “standardized 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.

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 or serious 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 14.

Table 14: 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

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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

CDTL Comment:

It is clear that higher exposures to OCA are associated with increases in serum transaminases and bilirubin in both the nonclinical and phase 1 studies. Liver injury was seen with exposures 12 times the expected human exposure in the dog toxicity studies (See Section 4 on page 12). Hepatic related adverse reactions also appear to occur at an increased frequency with increasing dose from the analysis of the combined data from phase 2 and 3 studies. It is also apparent that patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis have higher (17 times in advanced cirrhosis) exposures to OCA and these exposures overlap the exposures that induced hepatic injury in the nonclinical studies (See Section 5 on page 14). Therefore the reduced dose of OCA as recommended by the Clinical Pharmacology team will be recommended in the labeling. Patients with cirrhosis or advanced stage disease by the Rotterdam criteria should be monitored closely with initiation and during treatment with OCA. The Division will request a PMR under that accelerated approval pathway for additional safety, efficacy and steady state PK in patients with cirrhosis.

8.5 Dyslipidemia

CDTL Comment:

Integrating the data from the phase 2 trials the phase 3 trials and trials in other indications (see Clinical Review by Dr. Ruby Mehta), it is apparent that OCA induces changes in cholesterol metabolism that, as we understand the current data would indicate a potential for increased cardiovascular risk. Longer term follow up from the phase 4 confirmatory trial and the open label extension trials should provide further data on the rates of adverse events.

(b) (4)

8.6 Safety Summary

For a rare disease drug exposure was adequate to assess safety and efficacy based on the biomarker response. There were no major safety concerns that would preclude approval of OCA. The most common adverse event is pruritus which is already present in the underlying disease and patients with severe pruritus were excluded from the clinical trials. Interventions for pruritus of bile acid sequestrants or antipyretic agents or dose modification were usually successful in mitigating pruritus. However, pruritus may limit OCA use in some patients. Fatigue was also a common adverse event which is also common in the underlying disease.

Changes in lipid metabolism have been seen with OCA use through all clinical trials. There are mild increases in LDLc and mild to moderate decreases in HDLc. Some patients have significant alternations in lipid metabolism. It is unknown at this time if these

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changes will increase cardiovascular events. All patients on OCA should have their cholesterol panel monitored a few months after initiation of treatment and periodically thereafter.

OCA is known to cause liver injury at high exposures in the nonclinical studies and in the phase 1 trials in healthy volunteers. Patients with hepatic impairment secondary to cirrhosis can have exposures as high as or higher than the NOEAL seen in the dog toxicology study that was associated with hepatobiliary injury. Patients with cirrhosis should be dosed at the decreased dose recommended in the labeling and monitoring closely for evidence of hepatic injury. All patients receiving OCA should be monitored for evidence of hepatic injury.

9 Advisory Committee Meeting

An Advisory Committee Meeting was held on April 7th 2016. See the Appendix for the meeting minutes.

In Summary, the advisory committee supported the approval of OCA for treatment of PBC and felt that there was adequate evidence to support the use of ALP reduction as a surrogate reasonably likely to predict clinical benefit. The committee supported the proposed dose and the reduced dose for patients with hepatic impairment.

The committee felt there was adequate data to support use of OCA as monotherapy in patients intolerant or with an inadequate response to UDCA, but supported further study in this group. The committee was divided on supporting treatment for patients with moderately advanced and advanced hepatic impairment.

Discontinuing therapy with OCA when patients are not responding was discussed. Modifications to the design of the phase 4 confirmatory trial or other post-marketing trials were discussed and the committee agreed that more data was needed in patients with advanced disease by the Rotterdam criteria and in patients with hepatic impairment.

10 Pediatrics

This is an orphan drug and is therefore exempt from PREA requirements. PBC is an adult disease.

11 Other Relevant Regulatory Issues

There were no significant conflicts noted in the financial disclosures. The application for exclusivity has been submitted.

The studies were conducted under GCP standards.

From the review of Susan Leibenhaut, MD and Susan D. Thompson, M.D., Team Leader from Good Clinical Practice Assessment Branch, Division of Clinical Compliance, Evaluation Office of Scientific Investigations, Office of Compliance review dated February 12th, 2016, noted that six clinical investigator sites and the Applicant were inspected for this application. The classification for the

routine applicant inspection for this new molecular entity is pending. Four of the inspections have a final classification of NAI. The isolated instances of dosing error are not considered systemic or systematic. The violations cited for the VAI classifications at the applicant and at the clinical sites of Drs. Schiffman and Kowdley sites are considered minor. The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

Division of Risk Management (DRISK) review (April 12th, 2016) by Erin Hachey Pharm D. and Jamie Wilkins Parker, Pharm D., concluded that at this time, risk mitigation measures beyond labeling are not warranted for obeticholic acid for the treatment of PBC.

11.1 Design of Phase 4 – Confirmatory Clinical Benefit Trial

From review by Benjamin Vali – mathematical statistician

Study 747-302 is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter, multinational (in approximately 170 investigational sites) study evaluating the effect of OCA on clinical outcomes in patients with PBC. The lone primary objective of this study is to assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in patients with PBC as measured by time to first occurrence of any of the following adjudicated clinical events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥ 15 (this indicates the need for liver transplantation)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
 - o Variceal bleed
 - o Encephalopathy (as defined by a West Haven score of ≥ 2)
 - o Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (i.e., diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

The above composite event endpoint is the pre-specified primary endpoint of this study, and every previously specified/listed clinical event for participating patients will be adjudicated by an independent committee (see below for more details regarding this adjudication). The key secondary objectives of this study are to assess the effect of OCA compared to placebo on time to first

occurrence of each individual component of the primary composite event endpoint as listed above and to also include liver-related death. Note that the formally pre-specified key secondary endpoints are listed in the order that follows:

- Time to first occurrence of MELD score ≥ 15
- Time to Liver Transplant or Death (all cause)
- Change from Baseline in TB at end of study (EOS)
- Change from Baseline in ALP at EOS

An additional secondary study objective is instituted, for supportive analysis purposes, to provide further comparative evaluation of the clinical benefit of OCA. The effect of OCA will be compared to historical controls (separately and in combination) on liver-related clinical outcomes (i.e., death or liver transplant). These historical controls will be made available from the historical PBC observational databases of the United Kingdom (UK)-PBC and Global PBC Study Groups. Each database includes approximately 5000 patients with long-term follow-up.

The two most significant inclusion criteria for determining study eligibility pertain to the aforementioned pre-treatment assessed ALP and TB values along with allowing concomitant usage of UDCA while participating in this study. Specifically, these two inclusion criteria, respectively, are as follows:

- Have at least one (i.e., “and/or”) of the following qualifying biochemistry values (representing the mean of all available screening values)
 - o ALP $> 5 \times \text{ULN}$
 - o TB $> \text{ULN}$ but $\leq 3.0 \times \text{ULN}$
- Taking UDCA for at least 12 months (with a stable dose for at least 3 months) prior to study start, or unable to tolerate UDCA (i.e., no UDCA usage for at least 3 months) prior to study start.

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

- Pretreatment TB ULN category ($> \text{ULN}$, $\leq \text{ULN}$)
- Intolerance to UDCA; (‘no’ hence UDCA usage for at least 12 months, with a stable dose for at least 3 months, prior to study start with the assumption of continued stable usage of UDCA throughout the study, ‘yes’ hence no UDCA usage for at least 3 months prior to study start with the assumption of continued non-usage of UDCA throughout the study).

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years (which includes 2 years of accrual and 6 years of follow up)
- 5% of the patients having never been treated with UDCA; 95% of the patients having been on UDCA for at least 1 year
- Patients being randomized in a 1:1 ratio to placebo or OCA
- The 2 groups being compared using a 2-sided log rank test at the 5% level of significance.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (from both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on the time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 patients (i.e., 175 per treatment arm) will be enrolled to attain 121 events.

Statistical Reviewer (Ben Vali) Comments:

The sample size calculation could not be validated. Based on the assumptions given above, it was estimated by the statistical reviewer that approximately 436 patients (i.e., 218 per treatment arm) would need to be enrolled to attain 121 events.

Throughout the execution of this protocol, an independent data and safety monitoring committee (DSMC) will operate according to a DSMC Charter. It will provide an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there are no formally planned interim analyses for this study.

If after four years of accruing patients, despite increases in the number of enrolled patients through the aforementioned sample size re-estimation approach (described in Part II above), 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 sponsor 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 Group, 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, the propensity score matching technique, will be utilized. Specifically the calculated propensity score quintile number will be used as an additional factor/dependent variable in the primary endpoint analysis method, as described above, for comparing these combined groups in regards to time to liver transplant or death (all-cause).

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Historical control patients from both the UK-PBC and Global PBC Study Group databases will be chosen based on the same 747-302 trial inclusion/exclusion criteria where possible. Both the UK-PBC and Global PBC Study Groups formally collected numerous covariates that could be related to treatment assignment, and hence used for propensity score estimation, including standard of care (i.e., UDCA). A propensity score for each patient will ultimately be estimated by using these available covariates that may be predictive of treatment assignment.

CDTL Comment:

The phase 4 trial as designed may not include adequate numbers of patients with all stages of PBC to adequately describe and verify the clinical benefit in all stages of the disease. We have addressed this issue with the Applicant in a PMR #3 (See below).

12 Labeling

Prescribing Information

The labeling as proposed by the Applicant was edited by the team while the Applicant has agreed to the majority of the changes, at the time of this review, they have not review Section 14 which was written later that the other sections of the labeling. Labeling negotiations were still ongoing at the time of this review.

The team elected to write the labeling in such a way as to not make rigid definitions of the biochemical responder criteria (ALP and/or TB cut-off levels or the amount of change in ALP and TB) that either makes patients eligible for treatment with OCA or are used for decisions to up titrate patients from 5 to 10 mg.

- INDICATIONS AND USAGE section:

The team also elected not to place any limitations of use for OCA despite the significant data on patients with cirrhosis. The team agreed that the dosing recommendations and warnings and advice for monitoring patients was adequate to protect patients and the risk/benefit favored allowing use of this drug for patients with an unmet medical need and life-threatening disease.

- DOSAGE AND ADMINISTRATION section:

We agreed with the Applicants proposal to start all patients at the 5 mg dose and up titrate at 3 months if there was an inadequate biochemical response in ALP and TB. The data supported that there may be less pruritus and better tolerance with the lower starting dose.

The team elected to make recommendations to up titrate the dose at 3 months based on the data from the clinical trial that indicated the majority of patients that were going to have a biochemical response would do so by 3 months.

We also elected to stay silent of the question of discontinuing drug for lack of biochemical response. While this issue was discussed at the AC meeting and the clinical pharmacology team make recommendations that the drug be discontinued if there was no response in ALP or TB after 6 months of treatment at an adequate. We felt that some patients may have an incomplete response and this decision was best handled between patients and doctors until more data could be obtained on the risk/benefit of continued treatment in the phase 4 confirmatory trial.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
The team did not think the safety issues raised to the level of a boxed warning, however, the potential for liver injury, dyslipidemia and pruritis were all placed in the warning and precautions section.

- CLINICAL STUDIES section:

(b) (4)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE) dated February 22, 2016 by Matthew Barlow, RN, BSN and Mishale Mistry, PharmD, MPH recommended revisions to the container labeling that were performed by the Applicant and the changes were acceptable to the team.

The Division of Pediatric and Maternal Health was consulted for labeling and the consult dated November 20th, 2015 by Christos Mastroyannis, MD noted several changes to the labeling, these were negotiated with the Applicant and finalized.

Meeta Patel, PharmD., Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP) (April 29th, 2016) reviewed the labeling and recommendations were made for changes, the team agreed with the recommendations.

13 Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There was no significant risk requiring a REMS for this application.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The PMRs are requested under the accelerated approval rule. The Applicant has proposed the timelines as noted below. The final approval of these timelines by the Division has not been made at the time of this review.

PMR 3057-1

Description:

A randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady-state pharmacokinetics of obeticholic acid in patients with primary biliary cholangitis/cirrhosis (PBC) with Child-Pugh Classes B and C hepatic impairment, including Child-Pugh Class C patients with varying levels of MELD scores. You may conduct this as a stand-alone trial or in a subset of patients in your confirmatory trial (PMR# 3057-3).

PMR 3057-1 Schedule Milestones:

| | |
|----------------------------|------------|
| Final Protocol Submission: | 12/01/2016 |
| Study/Trial Completion: | 12/01/2022 |
| Final Report Submission: | 04/01/2023 |

PMR 3057-2

Description:

This was a randomized, placebo-controlled trial to evaluate the safety and efficacy of OCALIVA used as monotherapy in patients with primary biliary cholangitis/cirrhosis (PBC) who are intolerant of or non-responsive to ursodeoxycholic acid (UDCA). Enroll patients across all stages of PBC, by the Rotterdam criteria. You may conduct this as a stand-alone trial or in a sub-set of patients in your confirmatory trial (PMR # 3057-3).

PMR 3057-2 Schedule Milestones:

| | |
|----------------------------|------------|
| Final Protocol Submission: | 12/01/2016 |
|----------------------------|------------|

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Study/Trial Completion: 12/01/2022
Final Report Submission: 04/01/2023

PMR 3057-3

Description:

A randomized, double-blind, placebo-controlled trial to verify and describe that OCALIVA-induced reductions in alkaline phosphatase and/or total bilirubin are associated with improvements in the composite clinical endpoint of progression to cirrhosis, death, transplant, decompensation events and hepatocellular cancer. Your ongoing trial (747-302) should be revised to include patients across the spectrum of stages of primary biliary cholangitis/cirrhosis (PBC), including patients with early, moderately advanced and advanced PBC by the Rotterdam criteria, and should be adequately powered to demonstrate benefit in each stage.

PMR 3057-3 Schedule Milestones:

Draft Amended Protocol Submission 09/01/2016
Final Protocol Submission: 12/01/2016
Study/Trial Completion: 12/01/2022
Final Report Submission: 04/01/2023

PMC 3057-4

Description:

Develop a formulation that would allow once daily dosing for patients with hepatic impairment. Conduct a (b) (4) study in healthy subjects to characterize the (b) (4) bioavailability of the new formulation. Submit your (b) (4) study protocol once you have a new formulation.

PMC 3057-4 Schedule Milestones:

Final Protocol Submission: 11/01/2017
Study/Trial Completion: 04/01/2019
Final Report Submission: 08/01/2019

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CDTL Comment:

The PMRs are requested to be obtaining more data in specific subsets of the PBC population (i.e., monotherapy and patients with hepatic impairment) and also to be sure that the phase 4 confirmatory trial encompasses a population that will adequately represent the population who will receive the drug.

14 Recommended Comments to the Applicant

Further discussion with the Applicant on the design of the phase 4 confirmatory trial and the other post-marketing trials will take place in the near future.

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/s/

LARA DIMICK-SANTOS
05/25/2016