CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207999Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Dragos Roman, MD, Associate Director, Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 207999
Applicant Name	Intercept Pharmaceuticals, Inc.
Date of Submission	June 29, 2015
PDUFA Goal Date	February 29, 2015 amended to May 27, 2016.
Proprietary Name / **Established (USAN) Name**	OCALIVA (obeticholic acid)
Dosage Forms / Strength	5 mg and 10 mg tablets
Proposed Indication(s)	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.
Action/Recommended Action for NME:	Approval under accelerated approval (Subpart H)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ruby Mehta, M.D.
CDTL Review	Lara Dimick-Santos, M.D.
Statistical Review	Benjamine Vali, M.S., Min Min, Ph.D. ,Andrejus Parfionovas, Ph.D.,Yeh-Fong Chen, Ph.D.,Sue-Jane Wang, Ph.D.
Pharmacology Toxicology Review	Tracy Behrsing, Ph.D., Sushanta Chakder, Ph.D., Abigail Jacobs, Ph.D.
CMC Review	Ben Stevens, Ph.D., Hitesh Shroff, Ph.D.,Vaikunth Prabhu, PhD., Bryan Ryan, Ph.,D., Peng (Vincent) Duan, Ph.D., Truong Quach, Ph/D., Laura Pogue, Ph.D., Paul Perdue, Ph.D., James Laurenson, Ph,D.
Microbiology Review	
Clinical Pharmacology Review	Elizabeth Shang, Ph.D., Shen (Steven) Li, Ph.D., Sue-Chih Lee, Ph.D., Dhananjay Marathe, Ph.D., Nitin Mehrotra, Ph.D., Yuching Yang, Ph.D., Ping Zhao, Ph.D., Vikram Sinha, Ph.D., CAPT. E. Dennis Bashaw, Pharm.D.
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IRT	IRT Team

OSE/DMEPA	Matthew Barlow, RN, BSN, Kendra Worthy, PharmD, Todd Bridges, RPh

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DPMH- Division of Pediatric and Maternal Health
OPDP=Office of Prescription Drug Promotion
DBRUP=Division of Bone, Reproductive and Urologic Products
IRT=Interdisciplinary Review Team for QT studies

1. Introduction

In this New Drug Application (NDA), Intercept Pharmaceuticals Inc. is seeking approval of OCALIVA for the indication of "treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in (b) (4) unable to tolerate UDCA." The active ingredient in OCALIVA is obeticholic acid, an analog of the naturally occurring bile acid chenodeoxycholic acid (CDCA). Obeticholic acid is an agonist of the farnesoid X receptor (a nuclear receptor that regulates bile acid homeostasis) with an affinity estimated to be approximately 100-fold higher than CDCA. Obeticholic acid is a new molecular entity, and as such has not been approved for any other indication. In this memorandum, the term obeticholic acid will be used in reference to the active ingredient (drug substance) and OCALIVA (or OCA for simplicity) in reference to the drug product.

OCA is manufactured as tablets containing 5 mg or 10 mg of obeticholic acid, to be administered orally once daily. The Applicant is proposing a dosing regimen starting with a dose of 5 mg daily followed by titration up to 10 mg daily based on tolerance to the medication (primarily pruritus) and biochemical response.

Obeticholic acid was granted orphan drug designation by the Office of Orphan Products Development (OOPD) on April 9, 2008, and received fast track designation on May 27, 2014; subsequently DGIEP agreed to receive the NDA on a rolling basis with the final component of the NDA having been submitted on June 29, 2015.

The application was reviewed under a priority review clock. A major amendment was issued on October 27, 2015, in order to allow the review of additional data that the FDA felt to be necessary for the approval of this application; it extended the goal date by three months. An Advisory Committee meeting was held on April 7, 2016.

2. Background

Primary Biliary Cirrhosis (PBC), recently renamed as Primary Biliary Cholangitis, is a chronic, cholestatic liver disease that exhibits a slow clinical progression extending over many decades. Early

on, patients are typically asymptomatic, and suspicion of a potential PBC diagnosis is raised by an elevation of alkaline phosphatase (ALP) noted on screening blood tests obtained during routine office visits. The age of initial diagnosis is typically between 40 and 60 years. Over time, PBC progresses to hepatic fibrosis, cirrhosis, hepatic decompensation, and eventually death. PBC is a rare disease (prevalence of 1.91 to 40.2 per 100,000 inhabitants) and affects predominantly women (10:1 women to men ratio).

The pathological progression in PBC starts with non-suppurative destruction of the small intralobular bile ducts (ultimately leading to ductopenia) followed by impairment of hepatic bile flow, increased intrahepatic bile concentrations with subsequent hepatic cell injury and hepatic fibrosis. Although the exact etiology and precise pathogenesis of PBC are not fully understood, PBC is thought to be an autoimmune disease. The serologic hallmark of PBC is the presence of antimitochondrial antibodies, which are seen in 90-95% of PBC patients. Diagnosis of PBC is typically confirmed when two of the following three criteria are met:

- biochemical evidence of cholestasis with elevation of ALP activity for more than 6 months
- presence of antimitochondrial antibodies
- histologic evidence of chronic non-suppurative cholangitis of small and medium size bile ducts (if a biopsy is performed).

Biochemically, PBC is associated with ALP elevations in early stages (increases in gamma glutamyl transpeptidase and transaminases are also seen) followed by elevations in bilirubin and or reductions in albumin as the disease progresses; in the end, as the hepatocellular mass is reduced, elevations in some of these biomarkers may reverse. Survival is affected in patients with PBC: once total bilirubin reaches 2 mg/dL mean survival is 4 years; it declines to 2 years when bilirubin reaches 6 mg/dL. Another biochemical manifestation is dyslipidemia, which has not been associated, however, with cardiovascular disease manifestations in PBC.

Clinical signs and symptoms of PBC include fatigue, pruritus and, later in the course of the disease, portal hypertension, cirrhosis-related signs, symptoms and complications (esophageal varices/bleeding, ascites, and hepatic encephalopathy). Autoimmune manifestations can accompany PBC, but will not be discussed here because obeticholic acid only targets the hepatic manifestations of the disease.

Ursodeoxycholic acid (UDCA) is the only pharmacologic agent approved for the treatment of PBC. It was approved in the US in 1997, and is currently standard of care. Therefore, the phase 3 clinical program was conducted in patients who failed to normalize biochemically on UDCA or in patients who could not tolerate UDCA (a minority of patients). It is estimated that up to 40% of UDCA-treated patients have a suboptimal response to UDCA and, as such, are at an increased risk of an adverse outcome due to disease progression.

The regulatory history of the OCA program is long and complex (refer to the CDTL review for details). Given the long and slow progression of the disease and the wide spectrum of manifestations, there have been significant challenges to planning and conducting a successful clinical program in patients with PBC. From the beginning, FDA emphasized the limitations of using a biomarker (such as ALP) as a primary efficacy 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 a clinical benefit (i.e., an improvement in how patients feel, function or survive). Therefore, the Division did not agree that ALP would be considered an appropriate endpoint to demonstrate clinical efficacy of OCA in PBC, unless additional data will be submitted to support this choice of endpoint. FDA advised Intercept to investigate the relationship between PBC biomarkers (such as ALP and bilirubin) and clinical outcomes.

Based on this advice, Intercept helped establish and subsequently collaborated with the Global PBC Study Group, an academic independent research group founded in January 2012, whose principle investigators are located at the Erasmus MC University Medical Center in Rotterdam, Netherlands. The Global PBC Study Group has compiled data from approximately 5,000 adult PBC patients into a multinational, multicenter registry. The data are primarily retrospective but, importantly, they include clinical outcome information (death or liver transplant). The PBC Study Group data were evaluated for a possible relationship between biomarker data (ALP and total bilirubin) and a clinical outcome (death or hepatic transplantation). Data from this international registry indicated that a reduction in elevated levels of ALP and total bilirubin at 12 months is associated with a favorable outcome (transplant-free survival)[1]. The applicant subsequently leveraged the results from this independent study to construct a composite endpoint that was used in the phase 3 study 747-301.

There are two issues that are central to this NDA. First is the question whether the OCA clinical program has demonstrated efficacy relative to placebo and a favorable overall safety profile. The second issue is related to the use of a biomarker (ALP) as an efficacy endpoint throughout the entire phase 2 and phase 3 clinical programs, and whether ALP can be considered an endpoint reasonably likely to predict clinical benefit, a regulatory requirement for an accelerated approval under 21 CFR 314 Subpart H of the Food, Drug, & Cosmetic Act. Both questions will be addressed in detail in this memorandum.

3. CMC/Device

I concur with the recommendation for approval issued by the OPQ reviewers who conclude that the applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. An "Approval" recommendation was issued by the Office of Facility and Process regarding the facilities involved in this application. There are no outstanding issues and no recommendations for phase 4 PMRs or PMCs. A claim for Categorical Exclusion for the Environmental Assessment was granted.

The drug substance in OCALIVA is 6α-ethyl chenodeoxycholic acid (USAN name: obeticholic acid). OCALIVA is manufactured in a tablet form containing either 5 mg or 10 mg of the obeticholic acid. The inactive ingredients are microcrystalline cellulose (b) (4), sodium starch glycolate (b) (4), and magnesium stearate (b) (4); all these ingredients are compendial. Similarly, the coating material (Opadry II Yellow) contains acceptable ingredients. The container closure system (a 40 cc polyethylene bottle holding 30 tablets, closed with a seal and a polypropylene child resistant cap) was found acceptable (b) (4) in long-term and (b) (4) testing.

(b) (4)

[1] Lammers et. al., Levels of Alkaline Phosphatase and Bilirubin Are Surrogate End Points of Outcomes of Patients With Primary Biliary Cirrhosis: An International Follow-up Study. Gastroenterology 2014;147:1338–1349 .

(b) (4)

The identity, strength, purity and quality of the drug product were assured by adequate control of the raw material, a validated manufacturing process, and drug product specifications. The analytical methods used to measure product quality attributes were judged to be acceptable, as were the manufacturing process and the proposed in-process controls.

The stability data provided in the application support a 24-month expiration for OCA tablets when stored in the proposed container closure system. The drug product stability testing demonstrated that there was no degradation in the product quality for this period of time.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers. There are no outstanding pharm/tox issues that preclude approval, and nor recommendations for PMRC/PMCs.

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

Repeat-dose oral toxicity studies completed in rodents and non-rodents identified the hepatobiliary system as a site of toxicity. Elevations in liver enzymes (ALT, AST, and ALP), bile duct hyperplasia, and hepatocellular hypertrophy were seen in rodents in a 26-week oral toxicity study. Similarly, elevated ALTs were seen in a 9-month oral toxicity study in dogs, along with clinical signs consistent with alterations in liver function (yellow discoloration of the skin, mucous membranes, and eyes). The clinical relevance of these hepatic toxicity finding will be further discussed in the Safety Section of this memorandum (hepatic adverse events have been seen in the clinical program at doses in excess of the maximum to-be-marketed dose of 10 mg).

Of note, these nonclinical observations were made at exposures above those expected to occur with the doses that will be marketed in humans. The rat NOAEL derived from the 26-week toxicity study (6 mg/kg/day) was estimated to produce systemic exposures approximately 2.3 times higher than those expected to be seen in humans at the maximally recommended human dose (MRHD). Similarly, the 15 mg/kg/day NOAEL from the 9-month repeat-dose toxicity study in dogs was estimated to produce systemic exposures approximately 12 times those in expected in humans at the MRHD.

Obeticholic acid and its conjugates (glyco-OCA and tauro-OCA) were not found to be genotoxic or clastogenic across several in vitro assays (Ames test, human peripheral blood lymphocyte chromosomal aberration test, and mouse micronucleus test). There was no evidence that obeticholic acid may be carcinogenic. In a 2-year oral carcinogenicity study in mice, no obeticholic acid-related neoplastic findings were identified at doses up to 25 mg/kg/day (12 times higher exposure that human exposure at the MRHD). In a rat 2-year oral carcinogenicity study conducted at a daily obeticholic acid dose of 20 mg/kg/day (a little less than 12 times the human exposure at MRHD) there were no drug-related neoplastic findings in males; there was an increase in the incidence of benign granulosa cell

tumors in the ovaries and benign granular cell tumors in the cervix and vagina that were found in females. This information will be described in the agreed label.

The reproductive and developmental toxicology program did not raise any specific concerns. Adverse events were observed in animals at exposures higher than the anticipated exposure for the MHRD (e.g.: 13 times higher in an oral fertility and early embryonic development study; approximately 40 times in an embryofetal development study in rats, and 6 times in an embryofetal development study in rabbits; 21 times in a pre- and postnatal development study in rats).

Drug substance impurities were qualified and within acceptable limits; the proposed specifications for elemental impurities, residual solvents, were found to be acceptable.

The proposed established pharmacologic class, farnesoid X receptor agonist, is acceptable to the reviewers.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology/biopharmaceutics reviewers conclude that there are no outstanding clinical pharmacology issues that preclude approval.

The applicant conducted a wide range of studies including PK/PD evaluations in healthy volunteers and patients with PBC, drug-drug interaction studies, a thorough QT study, hepatic impairment and food-effect studies, as well as exposure-response analyses for efficacy and safety, and physiological PK modeling and simulations. The totality of these data supports the proposed dosing, and will be discussed further.

The phase 3 clinical trial established efficacy and safety of two different dosing regimens: a 10 mg fixed dose and a titration regimen starting at 5 mg and advancing to 10 mg based on clinical and biochemical response. Both dosing regimens were similarly effective in reducing alkaline phosphatase, but the titration regimen was associated with better tolerability, and should be the preferred dosing regimen for labeling. For instance, discontinuations related to pruritus, a consistent tolerability issue seen during the OCA clinical program, were largely prevented with the titration regimen (only 1% of all patients discontinued due to pruritus) when compared to the fixed dose regimen (10% pruritus-related discontinuations). In addition, some patients seem to respond biochemically at the 5 mg dose, and therefore it is reasonable to continue this regimen given the better tolerability. Another observation made during the analysis of the efficacy results of trial 747-301 is that the reduction in ALP was sees as early as 2 weeks, and was clearly established by 3 months of treatment in patients who responded to the drug; therefore, although in the phase 3 trial patients were uptitrated at Month 6, there is no reason to wait so long, and an earlier uptitration timepoint should be labeled (3 months).

Although the maximum daily dose tested in the phase 3 clinical program was 10 mg, higher OCA doses were evaluated in the phase 2 program. Observations made in two phase 2 clinical trials indicated that 1) daily doses greater than 10 mg (25 mg and 50 mg) do not offer any efficacy advantage with respect to ALP reduction, and 2) daily doses in excess of 10 mg were associated with poor tolerability and a potential liver safety signal (see Safety Section for details). Therefore, the 10 mg daily dose should be the maximum approved and labeled dose.

A food effect study showed only small differences in plasma exposure of OCA and its two active metabolites (glyco-OCA and tauro-OCA) between fed and fasting conditions. These differences are

not clinically meaningful, particularly in the context of a titration regimen. Therefore, the same dose of OCA should be labeled for administration regardless of meal timing.

Drug-drug interactions were extensively evaluated in the OCA clinical pharmacology program both *in vitro* and *in vivo*. OCA is not a substrate of CYP enzymes (once absorbed, it is conjugated in the liver to glyco-OCA and tauro-OCA, both of which are metabolically active); therefore the PK of OCA should not change either by auto-induction or auto-inhibition.

Based on the *in vitro* and *in vivo* findings, there appears to be potential for OCA to increase the systemic exposure to drugs that are CYP1A2 substrates. Although in vitro studies did not show a clear CYP1A2 inhibition, in an *in vivo* study, 10 mg OCA increased systemic exposure to caffeine (a CYP1A2 substrate) by 42%. The clinical pharmacology reviewer recommends that the label include this observation.

Data in the clinical program indicate that bile acid sequestrants will not interfere with absorption of OCA if they are administered 4 hours before or 4 hours following meals (for study participants who followed such an administration schedule, only modestly lower trough concentrations of OCA were observed at Month 6 and Month 12). This information will be included in the label. Similarly, a drug interaction with warfarin will also be labeled (International Normalized Ratio decreased following co-administration of warfarin and OCA).

Prediction models that incorporate liver function status indicate that no dose adjustment is necessary for the starting OCA dose when given to patients with mild hepatic impairment. However, the same models predict that in PBC patients with moderate and severe hepatic impairment will have 4- to 17-fold greater exposures to OCA. Given this prediction, and the observation of an increase in number of hepatic adverse events was seen at doses greater than 10 mg in the phase 2 program, it seems prudent that special dosing should be instituted for PBC patients with hepatic impairment. The clinical pharmacology team recommends that the starting dose of OCA for moderate and severe hepatic impairment (Child-Pugh B and C) should be 5 mg once weekly, rather than once daily. If an adequate reduction in alkaline phosphatase has not been achieved after 3 months at this starting dose, and the patient is tolerating the drug, the OCA dose should be increased to 5 mg twice weekly and then subsequently to 10 mg twice weekly depending on response and tolerability. (b) (4)

(b) (4)

No OCA dose adjustments are required in renal impairment. Urinary excretion of OCA is less than 3% after oral administration of [14C]- OCA, while about 87% is excreted in feces.

In a study conducted at a supratherapeutic dose of OCA (100 mg, the maximum tolerated dose, exposure of 5 days) no significant QTc prolongation effect was observed.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

7.1 Clinical Program Overview

The OCA clinical program included a single, 12-month, phase 3 clinical trial (747-301). The efficacy demonstrated in this trial was supported by two shorter (3-month) phase 2 clinical trials (747-201 and 747-202); all three trials were randomized, double blind, and placebo-controlled. The clinical program also included an open-labeled extension study in which durability of therapeutic effect was evaluated and confirmed. As already mentioned in the background section, the phase 3 clinical trial was designed with FDA input. The Phase 2/3 clinical program is summarized below.

	Phase 2 Studies		Phase 3 Study
	747-201	**747-202**	**747-301**
Total number of patients	59	138	216
Design	Placebo-controlled Randomized (1:1:1)	Placebo-controlled Randomized (1:1:1:1)	Placebo-controlled Randomized (1:1:1)
Ocaliva doses	10mg; 50 mg	10mg; 25 mg; 50 mg	10 mg; titration (5 mg to 10 mg)
PBC background therapy	None	UDCA*	UDCA (few patents were enrolled without UDCA treatment)
Primary efficacy endpoint	Percent change from baseline in ALP at Month 3**	Percent change from baseline in ALP at Month 3**	A composite endpoint including ALP and total bilirubin

* UDCA = ursodeoxycholic acid (approved therapy in PBC)
**ALP = alkaline phosphatase

7.2 The OCA Phase 2 Program

The phase 2 clinical trials, although similar in design (dose-ranging, randomized, placebo-controlled), duration (3 months) and range of OCA doses (10 mg to 50 mg once daily), were conducted in two different PBC patient groups: in Study 747-201 patients did not receive UDCA as background treatment (i.e. they received OCA monotherapy); in Study 747-202 OCA was administered in addition to UDCA (add-on to standard of care). The inclusion criteria (very similar across both trials) allowed enrolment of a PBC patient population described as “early stage PBC,” characterized by elevated ALP and mostly normal total bilirubin. This is important in interpreting the trial results because PBC encompasses a much wider spectrum of disease.

The monotherapy trial 747-201 showed a statistically significant decrease in mean ALP in both dose groups relative to placebo: the OCA 10 mg group showed a mean reduction from baseline in ALP of 44.5%; the 50 mg group showed a 38% mean reduction from baseline, while the placebo group remained practically unchanged. In this small clinical trial, the 50 mg dose did not appear to offer evidence of efficacy over the 10 mg dose, and was less well tolerated (pruritus was frequently reported). Similar results were observed for the OCA add-on trial 747-202, in that there was no evidence for a better biochemical response with the 25 and 50 mg OCA dose over the 10 mg dose. Treatment with all three doses resulted in similar mean and median reductions of alkaline phosphatase

relative to baseline (21-27%), while the placebo arm showed a negligible reduction of 3%. As seen in trial 747-201, pruritus was the most common treatment-emergent adverse event; in addition there was an imbalance in several hepatic adverse events (new onset jaundice, variceal bleeding, worsening of hepatic biochemistries), relative to placebo in the 25 and 50 mg OCA doses (hepatic adverse events will be discussed later in this memorandum).

In conclusion, the phase 2 program demonstrated statistically significant reductions in alkaline phosphatase relative to placebo when OCA was used as monotherapy and as add-on to the UDCA standard of care. The phase 2 program also demonstrated that doses greater than 10 mg (up to 50 mg) were not associated with better efficacy, and had worse tolerability (pruritus) and potentially higher rates of hepatic adverse events (seen mostly at doses greater than 10 mg). Data collected in these two phase 2 dose-response trials informed dose selection (10 mg) for the Phase 3, "pivotal" clinical trial.

7.3 The OCA Phase 3 Program: Trial 747-301

Trial 747-301 is an adequate and well-controlled clinical trial, and provides the main evidence in support of effectiveness for OCA in the treatment of patients with PBC at the dose intended for marketing (up to 10 mg daily).

Trial 747-301 was a three-arm, randomized, placebo-controlled, clinical trial of 12 months duration followed by an open-label, long-term, extension study. In addition to a placebo arm, trial 747-301 included two treatment arms that evaluated two different OCA dosing regimens: a fixed daily dose of 10 mg (similar to the 10 mg regimen of the phase 2 studies), and a titration arm in which OCA treatment was initiated at a lower dose (5 mg) that was up- titrated to 10 mg at Month 6, depending on patient's tolerance to treatment and biochemical response. The trial enrolled 216 patients (approximately 70 per arm). Although the vast majority of patients received UCDA background therapy, the trial allowed enrollment of a small number of patients (n=16) who could not tolerate UDCA, and therefore received OCA as monotherapy. To ensure balanced distribution of this subgroup of patients among treatment arms, patients were stratified at randomization. Another criterion for stratification was related to the severity of patients' initial biochemical characteristics (ALP, total bilirubin and liver enzymes).

Most patients enrolled in clinical trial 747-301 had early stage PBC. They were enrolled based on abnormal liver chemistries (specifically: ALP $\geq$ 1.67x upper limit of normal (ULN); total bilirubin greater than the ULN but below 2x ULN). However, because the inclusion criteria specified that PBC patients had to have an elevated ALP **or** an elevated total bilirubin, patients could be enrolled with an abnormality in only one of these analytes. This led to enrollment of a PBC population with elevated ALPs but with mostly normal bilirubin levels. Specifically, the mean ALP level at baseline was elevated at 323 U/L (corresponding to 2.7X ULN; all but 2 patients had ALP $\geq$ 1.67x ULN), while the mean total bilirubin of 11 µmol/L was within the normal range of 2 – 39 µmol/L, and 198/216 (92%) of patients had bilirubin in the normal range at baseline. Therefore, it is important to recognize that the results of clinical trial 747-301, not unlike the results of the phase 2 OCA trials, reflect primarily the response to OCA of patients with relatively milder forms of disease, or "early stage" PBC. The subgroup of patients with both abnormal ALP and total bilirubin (patients with more severe biochemical manifestations) is small, and provides only a limited number of observations.

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

- ALP below 1.67×ULN at Month 12 **and**
- a reduction of ALP ≥ 15% at Month 12 **and**
- total bilirubin < ULN at Month 12

Because 92% of patients were enrolled with normal bilirubin, the primary endpoint evaluated in essence changes in only 2 of the 3 criteria, both related to changes in alkaline phosphatase. This limitation and its implication will be discussed in Section 7.5, below. Of note, the 15% ALP reduction was added as a criterion to ensure that patients who were enrolled with ALP levels just above of the 1.67XULN threshold show at least this degree of ALP reduction.

The results of the pre-specified primary efficacy analysis conducted by the statistical team (Table 1, below) indicate that both OCA treatment groups were superior to placebo in the percentage of patients who achieved the pre-defined response.[2] This analysis allowed for sequential testing of the OCA arms. It is further supported by multiple sensitivity analyses (e.g., completer and per protocol analyses, and analyses that use different imputation strategies such as "worst case scenario" and "ultra-worse-case imputation," etc.). The FDA statistical reviewers were able to reproduce and confirm applicant's primary efficacy analysis.

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

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

Source: Reviewer's Table generated from ADLIVER dataset.
Note: Denominators for percentages are N.
[1]: A patient was designated as a responder if all three of the following conditions were met: (1) 12-Month value of ALP < 1.67×ULN; (2) 12-Month value of TB < ULN; (3) ALP reduction from baseline at Month 12 ≥ 15%.
[2]: Pair-wise comparison made between given OCA treatment group and Placebo adjusted for both randomization stratification variables.

The performance of the ALP assay was evaluated by the clinical pharmacology reviewer and found to be adequate. Given that this was a multinational trial, there were three regional laboratories, all accredited by their national authorities; one of the three labs was used as a reference lab as it had better precision and accuracy, and data from the other two labs were harmonized applying correction factors. Efficacy analyses were conducted with and without corrected factors, leading to similar results. The

[2] Table 1 is reproduced from the FDA Background Package for the April 7, 2016, Gastrointestinal Drugs Advisory Committee; the information in this table is also displayed in Table 4 of the FDA Statistical Review.

assays were commercially available assays; within run precision was < 5% and the accuracy for the assay kits was within 10%.

Additional categorical analyses using more stringent thresholds of response (e.g. 20%, 40% ALP reduction) showed consistent and similar differences across both OCA treatment arms vs. placebo. Several secondary and exploratory analyses evaluated other markers of cholestasis (GGT), markers of hepatocellular damage (ALT/AST), and markers of inflammation. All of them showed mean changes that consistently favored OCA relative to placebo. Of note, the baseline elevation of in GGT and the decline observed in the OCA arms paralleled the ALP findings, confirming that the source of elevated ALP was hepatic (to avoid potential confounding, the clinical trial excluded medical conditions that could result in an increase of non-hepatic ALP).

The statistical reviewer indicates that:

> Overall, the design of the 747-301 study was deemed as adequate and well-controlled from a statistical perspective, and the applicant's corresponding Statistical Analysis Plan (SAP) was adjudicated as being appropriate. There were no statistical review issues identified for this pivotal trial that would preclude product approval.

7.4 OCA as monotherapy

Since the number of patients treated with OCA as monotherapy in Trial 747-301 was small, the efficacy in this subgroup of patients could only be analyzed in a post hoc analysis that combined patients across phases 2 and 3 of the OCA clinical program. Table 46, reproduced below[3], suggests that the OCA treatment as monotherapy is similar to that seen as an add-on to UDCA. Therefore, it is reasonable to not restrict the indication to patients who received UDCA, and extend it to OCA monotherapy in patients who do not tolerate UDCA. This particular issue was discussed at the May 7, 2016, Advisory Committee meeting, and there was general agreement that this analysis provides preliminary evidence of effectiveness in this subgroup, but that additional data need to be collected in a confirmatory trial, should OCA receive accelerated approval. I concur with this approach, which is also recommended by the clinical reviewers.

[3] From Page 127 of the FDA briefing Document for the April 7, 2016 Gastrointestinal Drugs Advisory Committee meeting.

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

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

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

7.5 Alkaline Phosphatase as an Endpoint Reasonably Likely to Predict Clinical Benefit

During the development of the OCA program in PBC, FDA had multiple communications and face-to-face meetings with Intercept in which aspects of the clinical program such as trial design, dose selection, and acceptability of particular endpoints were discussed. Additional challenges in designing the OCA clinical program that were recognized early included the relative rarity of the disease (orphan disease), the broad spectrum of manifestations of PBC, and the long and slow progression of the disease. FDA has emphasized early in these communications the limitation associated with 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 there were no data to confirm that specific reductions in ALP (e.g. percent or absolute change) predict quantitative improvements in a clinical outcome such as survival, hepatic function improvement (e.g. reductions in portal hypertension, cirrhosis and associated complications), or health-related quality of life. Therefore, the Division did not agree that reductions of ALP alone would be considered sufficient to demonstrate clinical efficacy in the PBC clinical program, and recommended that additional data are needed.

The relationship between biomarkers and clinical outcomes in PBC has been an issue of interest to many investigators in this field. Efforts to correlate improvements or normalization of liver biochemistries (particularly ALP and total bilirubin) to clinical outcomes led to multiple investigations that, in the end, provided preliminary evidence of a link between ALP and/or bilirubin reductions and clinical response. Although individually most of these studies were too small to be considered convincingly predictive of an association with a clinical benefit, they provided similar evidence from multiple sources about certain thresholds of ALP response in PBC that could be used in designing a phase 3 clinical trial. Among such criteria, listed below, the "Toronto II" criteria (i.e., ALP ≤ 1.67×ULN and TB ≤ ULN[4]) appeared to be the most discriminating in predicting transplant-free survival; therefore these two cut-points were incorporated in the definition of clinical response for the the phase 3 program.

Response criteria

[4] ; Kumagi et al.: Baseline Ductopenia and Treatment Response Predict Long-Term Histological Progression in Primary Biliary. m J Gastroenterol 2010; 105:2186–2194; doi:10.1038/ajg.2010.216; published online 25 May 2010

Mayo 1999	Alkaline Phosphatase (ALP) <2 XULN
Barcelona 2006	> 40% decrease in ALP or normalization
Paris-1 2008	ALP < 3.0xULN, AST < 2.0xULN and total bilirubin (TB) ≤ 1mg/dL
Rotterdam 2006	Normalization of abnormal bilirubin and/or albumin
Toronto 2010	ALP ≤ 1.67xULN
Paris-2 2011	ALP ≤ 1.5xULN, AST ≤ 1.5xULN and bilirubin ≤ 1mg/dL
Mayo 2011	ALP ≤ 1.67xULN and total bilirubin ≤ 1mg/dL (ULN)

In addition, and importantly, the selection of these two thresholds leveraged also the results of the Global PBC Study Group analyses which provided the strongest evidence to date of a relationship between ALP/ total bilirubin reduction and an improvement in clinical outcomes (Lammers et al). In this publication, data from close to 5,000 adult PBC patients who had been followed until they achieved a clinical outcome of death or liver transplant were analyzed, and indicated that a reduction at 12 months of ALP, total bilirubin, or ALP and total bilirubin combined predicts transplant-free survival.

The totality of this information led to the selection of a responder definition in trial 747-301 that was based on a reduction in ALP below 1.67 XULN and of bilirubin <ULN (a 15% absolute reduction in ALP was added as a third criterion of response for reasons already explained). However, as described already, Study 747-301 ended up enrolling primarily patients with elevated ALP and normal total bilirubin (biochemical manifestations consistent mostly with early stage PBC). As such, leveraging the relationship between bilirubin and improvement in survival (bilirubin being the strongest predictor among of the two biomarkers according to the PBC Study Group data) was no longer appropriate. Another issue with relying on the PBC Study Group data is that the patient population of the PBC study group represents a broader spectrum of the disease, i.e., PBC patients having early, moderate, or even late stage disease). Finally, the vast majority of patients in trial 747-301 also received concomitant UDCA treatment, and this issue had to be addressed in assessing the relevance of the PBC Study Group data to the current NDA.

It is because of these unanticipated uncertainties that the FDA statisticians requested additional information from the PBC Study Group, which resulted in a major amendment to the application. Specifically, a subset of patients with similar characteristics to those of patients evaluated in clinical trial 747-301 was identified in the PBC Study Group database; this subset included 909 patients and 131 events of death or liver transplantation. After exploring multiple variables of interest, a statistical model was developed that incorporated age, baseline ALP values and % change in ALP at Month 12. The model looked at 17 different ALP cutoffs and evaluated the performance of the cutoffs with the highest C-statistic value (approximately 0.7) in multiple randomized subsets of the 909 patients referenced above. Subsequently these cutoffs (which consistently were associated with about 2.5-fold or greater hazard ratio for death and liver transplantation) were evaluated post hoc in a responder analysis in the 747-301 study patients, and showed statistically significant differences relative to placebo (refer to the statistical review for further details and discussion). Interestingly, the thresholds identified by the FDA statisticians and the ALP endpoints used in Study 747-301 performed comparably across both datasets.

In the end, these analyses (presented in detail in Dr. Min's review), provided not only evidence of the relevance of ALP, linking it to clinical outcomes in the large PBC dataset, but also showed consistency across multiple studies and independent datasets. They also provided additional statistical rigor to the PBC Study Group data.

It should be recognized that there are limitations to these data explorations. Given the retrospective nature of the data, these results should not be interpreted as a rigorous demonstration that ALP reductions predict improvements in transplant-free survival. They indicate however that ALP is more than a biomarker, and is can be seen as an endpoint that is reasonably likely to predict clinical outcome in PBC and, as such, supportive of an accelerated approval under Subpart H regulations for this condition. A confirmatory trial should be conducted to verify this reasonable assumption.

There are additional levels of evidence that support reliance on ALP in PBC. According to the currently available data, the site of initial injury in PBC is the small intrahepatic bile duct, and subsequent hepatic injury is due, at least in part, to the toxicity of accumulating intrahepatic bile acids. The choleretic effect of OCA combined with its effect on the bile acid synthesis (reduction of bile production and outflow from the hepatocyte) integrates the observed reduction in ALP into the pathophysiological context of the disease. It should also be stressed that the reductions in ALP are clearly OCA-related because they have not been seen in the placebo arm (in addition, OCA did not reduce ALP in healthy volunteers when administered chronically). Finally OCA's effect on ALP was consistent with other PD manifestations seen during OCA treatment: GGT reduction, AST/ALT reduction, as well as changes in fibroblast growth factor-19 , 7-alpha-hydroxy-4-cholesten-3-one (C4), and endogenous bile acids.

The issue of whether there is sufficient evidence that ALP in PBC can be considered an endpoint reasonably likely to predict clinical benefit (and therefore an appropriate endpoint to support a potential accelerated approval) has been discussed and met with concurrence from the Medical Policy Council.

8. Safety

The safety profile of OCA was in general acceptable, with no major safety signals identified in the current safety dataset which includes 232 patients exposed to therapeutic OCA doses for ≥ 12 months, and 70 patients for ≥ 2 years. The major safety observations were related to tolerability (pruritus), lowering of high density lipoprotein cholesterol (HDL-C) concentrations, and a slight increase in hepatic adverse event frequency which was seen mostly in the phase 2 program at doses in excess of the to-be-marketed 10 mg dose (none of these adverse events met the "Hy's law" definition) . The following is a brief description of these main safety findings.

Pruritus was the most common treatment-emergent adverse event (of note, an association between bile acids and pruritus is well established). It was not only a tolerability issue, but also severe enough to result in clinical trial discontinuation. Both the incidence and the severity of pruritus were dose-dependent. The significance of pruritus as a drug-related adverse event is further underscored by the fact that patients with severe pruritus due to their underlying PBC disease were excluded from the phase 3 trial. During the trial, patients who developed pruritus or had worsening of pruritus were offered treatment with bile acid sequestrants, anti-pruritic agents, or had a drug holiday or dose

reductions (e.g., dosing every other or every third day). The majority of patients were able to tolerate OCA with these interventions. Gradual titration of the OCA dose (as proposed in the final label) seemed to be mitigate pruritus to some extent.

Mean decreases in HDL-C were seen across all PBC clinical trials (about 10-20 mg reductions from a baseline of 70-80 mg/dl). These changes were still within the normal range, with a few patients showing declines below the lower limit of normal. The clinical significance of these changes, if any, is not clear at this time (the controlled data were no longer than 12 months, and there was no between-group difference in cardiovascular adverse events for this short duration of exposure).

A small imbalance in the incidence of hepatic adverse events relative to placebo was noted in a phase 2 trial which explored doses in excess of the to-be-marketed 10 mg dose (specifically, a 50 mg dose). Although these adverse events were consistent with complications expected to be seen in chronic liver disease (esophageal variceal bleeding, hepatic encephalopathy, ascites, cirrhosis flare, portal hypertension, jaundice, increase liver enzymes), it is reasonable to believe that this imbalance in hepatic AEs is a drug-induced effect given that similar observations were made in the nonclinical program (of note, there was no imbalance seen at the to-be-marketed 10 mg dose in the phase 3 trial). Consequently, hepatic adverse reactions should be labeled as a WARNING/PRECAUTION.

9. Advisory Committee Meeting

A Gastrointestinal Drugs Advisory Committee Meeting was held on April 7, 2016, to discuss this application. The efficacy and safety data from the obeticholic acid clinical program were discussed, along with a detailed presentation of the additional statistical analyses performed by the FDA to confirm the relationship between ALP changes at 12 months and outcomes of death and hepatic transplantation in the Global PBC Study Group. Following discussions, the Advisory Committee voted 17 to 0 when asked the following question:

> Taking into account the risks and benefit of OCA in the population studied, is there substantial evidence to support accelerated approval of OCA for the proposed indication, based on its effect on alkaline phosphatase?

The majority of the committee members agreed that a starting dose of 5 mg with titration up to 10 mg after 3 months is reasonable based on the data presented. Members commented that the increased incidence of hepatic adverse events is concerning, but it may be an acceptable risk given the benefit provided by OCA; they recommended that the confirmatory phase 4 trial(s) should attempt to better characterize hepatic adverse events, as well as monitor HDL cholesterol levels.

Committee members indicated that the limited amount of data in PBC patients treated with OCA alone appear sufficient to support the use of OCA as monotherapy under accelerated approval, but such patients should be further studied in the confirmatory trial.

The issue of OCA treatment in patients with moderately advanced or advanced stage PBC was discussed extensively. Most committee members agreed that there are limited data for patients with

moderately advanced stage PBC, and practically no data in advanced stage disease, but some supported the use of OCA in moderately advanced disease.

The majority of the committee commented on the insufficient data to support dosing of OCA in PBC patients with cirrhosis (Child-Pugh B and C), and called for additional postmarketing studies to characterize the dose in these subgroups.

Finally the majority of the committee members agreed that it may be premature to discontinue therapy after 6 months of OCA treatment even if there was no significant reduction in ALP.

10. Pediatrics

OCALIVA was granted Orphan Drug Designation. The requirements of the Pediatric Research and Equity Act do not apply to this application (in addition, PBC is an adult disease).

11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues.

12. Labeling

The label has been finalized at the time of this review. In summary, it includes a dosing regimen consistent with that evaluated in the titration arm of Study 747-301 (such a regimen seemed to be better tolerated with respect to pruritus, and also allowed flexibility of dosing). The only contraindication listed in the label is for patients with total biliary obstructions in whom stimulating choleresis is not expected to be beneficial for obvious reasons. Pruritus, hepatic adverse events, and HDL cholesterol reduction are listed as warnings and precautions with the goal of alerting the practitioner to these issues in order to integrate them in the overall patient care decisions.

Finally, the proprietary name, OCALIVA, has been accepted by the Division of Medication Error Prevention and Analysis (DMEPA)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval under Subpart H accelerated approval pathway. As discussed in the Efficacy Section of this memorandum, and as confirmed by the Gastrointestinal Drugs Advisory Committee vote of 17 to 0, there is enough evidence to conclude that ALP is an endpoint reasonably likely to predict clinical benefit in PBC. A confirmatory clinical outcome trial is currently ongoing. Although OCA was studied predominantly in “early disease stage” PBC, there is no reason to suspect that the disease process will

be qualitatively different in patients with more advanced stages of PBC associated with ALP elevations. Therefore the indication should not be restricted at this point to "early stage" PBC but the confirmatory trial should enroll both early stage and later stage(s) patients. This recommendation also acknowledges that criteria (such as the Rotterdam criteria used in the phase 3 trial) for separating "early" vs. "moderately advanced" and "advanced" but precirrhotic stages have incomplete ability to discriminate between these stages.

- Risk Benefit Assessment

The potential benefit of OCA therapy is best illustrated but the results of clinical trial 747-301, which showed an OCA-related reduction in percentage of responders at 12 months which was 3- to 4-fold higher than placebo (the persistence of treatment effect was confirmed for completers in an extension trial for up to 24 months of treatment). The threshold of response used in this clinical trial after 12 months of treatment (1.67X ULN) and other similar thresholds evaluated at the same 12-month timepoint have been associated in multiple datasets with a clinical benefit, such as transplant-free survival. In addition, this threshold and other related thresholds showed reasonable discrimination in predicting a favorable clinical outcome (hazard ratios > 2, and C-statistics close to 0.7). The preliminary evidence of biochemical and potential clinical response will require confirmation in a controlled, prospective clinical trial, expected to verify and describe the presumed clinical benefit.

It should be recognized that while OCA treatment does not address the fundamental cause of PBC (which remains to be confirmed at this time, with an autoimmune process being the most favored explanation currently), it is expected to modulate some of the intrahepatic processes that perpetuate the disease state once an initial injury is triggered. Down-regulation in the production of potentially hepatotoxic bile acids and reduction of their efflux from hepatocyte, along with promotion of choleresis, have the potential to limit hepatocellular damage and reduce the rate of hepatic deterioration.

Based on the currently available data, the risk associated with OCA therapy appears reasonable. The most concerning is the potential of liver associated toxicity, which was seen primarily at doses that exceed the maximum to-be-approved dose of 10 mg daily. Communicating this potential risk can be addressed by labeling this event as a WARNING/PRECAUTION, and recommending dose adjustment in patients with moderate or severe hepatic impairment.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The safety risks identified to date do not warrant a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

The following PMRs have been discussed and agreed across disciplines. They also reflect recommendations made at the April 7, 2016, Advisory Committee meeting. These PMRs address the need for a confirmatory clinical trial that is required under Subpart H regulations (Trial 3057-3; this trial should also include in its final protocol collection of pregnancy and infant data); as well as the need to further characterize the OCA treatment effect and safety profile in patients on monotherapy (Trial 3057-2) and in patients with hepatic impairment (Trial 3057-1).

3057-1 A randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady-state pharmacokinetics of OCALIVA (obeticholic acid) in patients with primary biliary cholangitis (PBC) with Child-Pugh Classes B and C hepatic impairment, including Child-Pugh Class C patients with varying levels of Model for End-Stage Liver Disease (MELD) scores. You may conduct this as a stand-alone trial or in a subset of patients in your confirmatory trial (PMR# 3057-3).

Final Protocol Submission:	12/16
Trial Completion:	12/22
Final Report Submission:	04/23

3057-2 A randomized, placebo-controlled trial to evaluate the safety and efficacy of OCALIVA (obeticholic acid) used as monotherapy in patients with primary biliary cholangitis (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).

Final Protocol Submission:	12/16
Trial Completion:	12/22
Final Report Submission:	04/23

3057-3 A randomized, double-blind, placebo-controlled trial to verify and describe that OCALIVA (obeticholic acid) 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 (PBC), including patients with early, moderately advanced and advanced PBC by the Rotterdam criteria, and should be adequately powered to demonstrate benefit in each stage.

Draft Amended Protocol Submission:	09/16
Final Protocol Submission:	12/16
Trial Completion:	12/22
Final Report Submission:	04/23

The following PMC was agreed with the applicant to develop a lower strength formulation that will better address a more convenient way of dosing in patients with hepatic impairment.

3057-4 Develop a formulation that would allow once daily dosing of OCALIVA (obeticholic acid) for patients with hepatic impairment. Conduct a study in healthy subjects to characterize the bioavailability of the new formulation relative to an approved formulation. Submit your study protocol once you have a new formulation.

Final Protocol Submission:	11/17
Study/Trial Completion:	04/19
Final Report Submission:	08/19

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/s/

DRAGOS G ROMAN
05/26/2016