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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	May 26, 2016
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	NDA 207999
Applicant Name	Intercept Pharmaceuticals, Inc.
Date of Submission	June 29, 2015
PDUFA Goal Date	May 29, 2016
Proprietary Name / Established (USAN) Name	Ocaliva/ obeticholic acid
Dosage Forms / Strength	Tablets/5 mg and 10 mg
Applicant Proposed Indication(s)	For the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. This indication is approved under accelerated approval based on [REDACTED] (b) (4) [REDACTED] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Action:	Approval
Approved Indication(s)/Populations	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. This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	Ruby Mehta, MD
CDTL Review	Lara Dimick, MD
Division Director Review	Dragos Roman, MD
Statistical Reviews	Min Min, PhD/Benjamin Vali, MS
Pharmacology Toxicology Review	Tracy Behrsing, PhD
CMC Review/ONDQA Review	Hitesh Shroff, PhD
ONDQA Biopharmaceutics Review	Peng Duan, PhD
Microbiology Review	Vaikunth Prabhu, PhD
Clinical Pharmacology Review	Elizabeth Shang, PhD
Pharmacometrics Reviewer	Dhananjay Marathe, PhD
DPMH	Christos Mastroyannis, MD (maternal health)
COA	Selena R. Daniels, PharmD, MS
OPDP	Meeta Patel, PharmD
DB VI	Yu-Ting Weng, PhD
OSI	Susan Leibenhaut, MD
OSIS	Melkamu Geti-Kebtie, PhD, RPh
OSE/DMEPA	Matthew Barlow, RN, BSN
OSE/DRISK	Erin Hachey, Pharm.D.
DBRUP	John Stinson, MD

CDTL=Cross-Discipline Team Leader
 CMC=Chemistry Manufacturing and Controls
 ONDQA=Office of New Drug Quality Assessment
 DPMH=Division of Pediatric and Maternal Health
 COA=Clinical Outcome Assessment
 OPDP=Office of Prescription Drug Promotion
 DB VI=Division of Biometrics VI
 OSI=Office of Scientific Investigations
 OSIS=Office of Study Integrity and Surveillance
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 DBRUP=Division of Bone Reproductive and Urologic Products

Benefit-Risk Summary and Assessment

Ocaliva (obeticholic acid) is an orally administered farnesoid X receptor (FXR) agonist. This memo documents my concurrence with the Division of Gastroenterology and Inborn Errors Products' accelerated approval recommendation for NDA 207999 for Ocaliva (obeticholic acid) tablets 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.

Efficacy was assessed in one 12-month, double-blind, placebo-controlled trial in 216 adult subjects with PBC randomized 1:1:1 to placebo, Ocaliva titration (5 mg with option to up-titrate to 10 mg after 6 months, if patient was tolerating the drug but not achieving an adequate response), or Ocaliva 10 mg. The primary efficacy endpoint was a composite of ALP and TB response criteria at month 12, which was based on disease prognostic risk criteria. A patient was designated a responder if all 3 of the following conditions were met:

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

Both OCA treatment groups showed a superior difference in the proportion of patients achieving response at month 12 when individually compared to placebo. The applicant sought to rely on evidence from the Global PBC Study Group, a large, multi-national retrospective cohort study of UDCA treated and untreated PBC patients across all stages (early, moderately advanced and advanced) of the disease, to support that these results are predictive of clinical benefit (transplant-free survival). However, because patients enrolled in the applicant's pivotal trial were almost exclusively in early stage PBC, FDA did not believe that the findings from the overall Global PBC Study Group could be relied upon to demonstrate the potential for clinical benefit with Ocaliva. Furthermore, because 92% of enrolled patients had a normal TB at baseline, the trial could not determine an effect of Ocaliva on TB or any contribution of TB to the composite endpoint. The FDA determined that the approval would need to rely solely on ALP, which would need additional support as a stand-alone surrogate endpoint reasonably likely to predict clinical benefit.

To explore the relationship between ALP and clinical benefit, the FDA analyzed data from a cohort of PBC patients (early stage and on concomitant UDCA) from the Global PBC Study Group. Using those data, FDA statistical reviewers were able to develop a statistical model with key covariates to establish ALP cut points that may predict clinical benefit (transplant-free

survival). FDA statistical reviewers then applied those cut points to a subset of subjects from the Ocaliva pivotal trial – those with TB within normal range and concomitantly receiving UDCA (n=181). Using the FDA’s stratified cut points, 5% of subjects in the placebo arm, 38% of subjects in the OCA titration arm, and 43% of subject in the OCA 10 mg arm achieved a response. Therefore, it was believed that the Ocaliva-induced reductions in ALP, which were over and above those achieved with UDCA alone, may provide a clinical benefit. However, additional supportive evidence needed to be considered. FDA comprehensively reviewed all available data to see if a case could be made for allowing use of ALP as a stand-alone surrogate endpoint reasonably likely to predict clinical benefit in PBC patients, within the context of the Ocaliva NDA. These data, which are discussed in my review, included the complementary mechanism of action of Ocaliva relative to UDCA; the biologic plausibility of Ocaliva’s effect on the pathogenesis of PBC; evidence from Ocaliva clinical trials that Ocaliva does what it is purported to do (agonizes FXR and reduces bile acid synthesis); clinical trial data on UDCA-induced reduction in ALP and its relationship to clinical benefit; epidemiologic data on UDCA-induced reduction in ALP and its relationship to clinical benefit; the natural history of ALP in untreated PBC patients; the lack of an effect of Ocaliva on ALP in healthy volunteers; the Ocaliva exposure-response relationship to ALP in PBC patients; the durability of the Ocaliva-induced ALP reductions; a determination that ALP reductions reflected liver-derived ALP; the performance of the ALP assay; and the intra-subject variability of ALP as observed in Ocaliva clinical trial populations. Overall, the data supported that Ocaliva demonstrates an effect of reducing liver-derived ALP in a statistically significant and clinically meaningful group of patients, and that these effects are over and above that which could be achieved with UDCA alone. This added effect is consistent with the mechanism of action of Ocaliva, and it is biologically plausible that Ocaliva may attenuate the hepatocellular damage induced by the accumulation of toxic bile acids. Further, it seems plausible, based on data observed with UDCA-induced ALP reductions of this magnitude, that Ocaliva may delay the progression of PBC to cirrhosis, need for liver transplantation, and death.

The safety of Ocaliva was assessed in 432 patients with PBC, including 290 who were treated with Ocaliva for at least 6 months, 232 who were treated for at least 12 months, and 70 who were treated for at least 2 years. Doses ranged from 5 mg to 50 mg once daily. Clinically significant liver-related adverse reactions (abnormal liver biochemical tests, ascites, new onset and worsening of jaundice, portal hypertension, PBC flare) were dose-related and occurred more frequently at doses that exceed the maximum recommended dose of 10 mg. Severe pruritus was reported more frequently in the Ocaliva-treated subjects relative to placebo; although, the incidence and severity of pruritus was attenuated by initiating subjects on a lower dose (5 mg) of Ocaliva, followed by titration to the 10 mg dose. Ocaliva treatment led to dose-dependent decreases in HDL-C levels. Despite these reductions, the majority of subjects remained within the normal range for HDL-C, although some Ocaliva-treated patients experienced quite profound decreases, to levels <20 mg/dL. The long-term risk of these reductions is

unknown, but should be considered in any decision to continue Ocaliva treatment in a patient who has not experienced a biochemical response to a maximally tolerated dose of Ocaliva by one year.

In coming to a decision to approve or not approve Ocaliva under an accelerated approval pathway, one must consider both the harms of approval should future studies fail to provide evidence of a clinical benefit, as well as the harms of non-approval should clinical benefit ultimately be demonstrated. In the former scenario, I have considered the harms of exposing patients to side effects (most notably severe pruritus, decreases in HDL-C, and liver-related SAEs), without prospect of benefit; the costs and inconvenience to patients associated with receiving treatment (drug costs, doctor visits, monitoring of laboratory tests), without prospect of benefit; and the possibility that providing treatment with Ocaliva with the belief that it is providing a clinical benefit may impede development of other, perhaps more promising, drug candidates due to patients' unwillingness to enroll in trials. On the other hand, I must consider that not approving Ocaliva will limit patients' treatment options to UDCA, to which ~40% of patients currently achieve an inadequate response; that waiting for completion of trials demonstrating a clinical benefit pre-approval may mean that an opportunity to alter the course of the disease in certain patients may be irreversibly lost; and that not approving Ocaliva may be denying patients access to a potentially life-saving therapy.

I have concluded that the applicant has provided convincing evidence that Ocaliva has a consistent and robust effect on reducing liver-derived ALP in PBC patients who do not adequately respond to UDCA; that the totality of evidence on reductions in ALP of this magnitude, in the setting of early stage PBC, supports its use as a surrogate endpoint reasonably likely to predict clinical benefit; that there are no concerning safety signals associated with the Ocaliva doses proposed for approval; and that the potential benefit of Ocaliva exceeds its risks. Approval of Ocaliva will help fill an unmet medical need for patients with this chronic life-threatening disease, who currently have limited treatment options.

There are many gaps in our understanding of Ocaliva, including its safety and efficacy in patients with moderately advanced and advanced stage PBC; its safety and efficacy in PBC patients with cirrhosis, both compensated and decompensated; the long-term efficacy and safety of Ocaliva as monotherapy; the effect of Ocaliva on TB levels, and how that effect should be factored into 'responder' algorithms for more advanced stages of PBC; and the benefits, if any, of continuing Ocaliva treatment in the absence of a biochemical response. The PI will acknowledge these gaps in our understanding, but I see no compelling reason to restrict such potential uses from the purview of the clinicians who manage these patients. Additionally, I firmly hope and expect that the sponsor will make a concerted effort to address these gaps in knowledge in the trials they

will be required to conduct to verify and describe the clinical benefit of Ocaliva.

Discussions regarding product labeling, and postmarketing study requirements and commitments have been satisfactorily completed. There are no inspectional issues that preclude approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Analysis of Condition</u></p>	<p>Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease, characterized by inflammatory destruction of interlobular and septal bile ducts. The disease disproportionately affects women versus men, approximately 10:1. It is typically diagnosed in patients between 40 and 60 years of age. The age-adjusted incidence of PBC in the U.S. is 4.5 per 100,000 women and 0.7 per 100,000 men, while the age-adjusted prevalence as of 1995 was 65.4 for women and 12.1 for men. PBC affects approximately 1/1000 women over the age of 40.</p> <p>The disease has a variable course, both in terms of symptomatology and rate of disease progression. The most common symptoms are fatigue and pruritus. Prognosis is worse for males, patients diagnosed at an earlier age, and patients who present with symptoms.</p> <p>Bile acids have long been known to facilitate digestion and absorption of lipids and to control cholesterol homeostasis. Endogenous bile acids, as chenodeoxycholic (CDCA), are potent signaling molecules through activation of the nuclear farnesoid X receptor (FXR). PBC is characterized by cholestasis with progressive impairment of bile flow in the</p>	<p>PBC is a chronic progressive life-threatening autoimmune cholestatic liver disease which significantly impacts a patient's quality of life. The disease is heterogeneous in presentation, both in terms of symptomatology and rate of progression. It disproportionately affects women. Patients diagnosed at an earlier age, and patients who have symptoms at the time of diagnosis, and male patients have a worse prognosis. Co-morbid conditions are common, in particular osteopenia/osteoporosis and hyperlipidemia. As many as 55% of female PBC patients will have a concomitant autoimmune disease. PBC is an important indication for liver transplantation.</p>

liver, resulting in increased hepatocellular bile acid concentrations. Bile acids are natural detergents, and abnormally elevated hepatocellular concentrations can be toxic to the liver. Such hepatocellular injury results in a local inflammatory response and is signaled early on by the secretion of alkaline phosphatase. In patients with an inadequate response to therapy, the disease frequently progresses to hepatic fibrosis, cirrhosis, hepatic decompensation, and death, in the absence of successful liver transplantation. Patients with advanced disease are also predisposed to hepatocellular carcinoma.

Diagnosis is based on a finding of at least 2 of the following 3 diagnostic factors:

- Biochemical evidence of cholestasis based on ALP elevation
- Presence of anti-mitochondrial antibody (AMA) titer or
- In the absence of AMA, liver biopsy consistent with PBC

While the cause of PBC is unclear, genetic predispositions have been described. It is believed that the disease may be triggered by a response to a number of factors, such as infection or chemicals, followed by an autoimmune response. Co-morbid conditions include osteopenia/osteoporosis, hyperlipidemia, and fat soluble vitamin deficiencies. Thirty-three to 55% of female patients will have concomitant autoimmune diseases, such as Sjogren's syndrome, Raynaud's syndrome, Hashimoto's thyroiditis, and psoriasis.

<p><u>Current Treatment Options</u></p>	<p>There is currently only one approved drug treatment for PBC, ursodeoxycholic acid (UDCA). UDCA was first approved in 1997 for the treatment of PBC. It is an orally administered hydrophilic bile acid administered at a dosage of 13-15 mg/kg/d. UDCA’s presumed mechanism of action is by changing the hydrophobicity index of the endogenous bile acid pool, decreasing the intracellular concentration of bile acids and favoring their elimination through the urinary route. UDCA has no significant FXR agonist properties. Up to 40 percent of PBC patients are un- or under-responsive to UDCA, and an additional 5 percent of patients are intolerant of the therapy, with side effects such as weight gain, gastrointestinal disturbance, or hair loss. Approximately 70% of the patients who present with PBC at a younger age, i.e., below the age of 30, will not respond to UDCA, whereas older presenting patients generally respond well.</p> <p>Transplantation can be effective as a salvage procedure, although it has a number of limitations. It is a high-cost Procedure, and it is associated with significant morbidity from the procedure itself, as well as from the immunosuppressive drugs required post-transplant. PBC recurrences post liver transplantation have been reported. Additional challenges relate to organ availability and access.</p> <p>AASLD (2009) recommends UDCA at a dose of 13-15 mg/kg/day for PBC patients at any stage of the disease as long as their liver biochemistries are abnormal.</p> <p>AASLD further recommends that pruritus be treated with bile</p>	<p>AASLD recommends the use of UDCA in the treatment of all patients with PBC who have abnormal liver chemistries. Up to 40% of PBC patients are un- or under-responsive to UDCA. There are no other approved therapies.</p> <p>Liver transplantation can be effective as a salvage procedure, although the procedure itself is associated with significant morbidity, and PBC can recur post transplantation.</p> <p>Symptomatic treatment of pruritus relies on the use of bile acid sequestrants, or the off-label use of rifampicin, oral opioid antagonists, or SSRI’s.</p> <p>Co-morbid osteopenia/osteoporosis is treated with bisphosphonates and vitamin D supplementation.</p> <p>There is a significant unmet medical need – both for alternative disease modifying agents, as well as more targeted treatment of the disease itself.</p>
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	<p>acid sequestrants as first-line therapy. Alternatively, rifampicin, oral opioid antagonists, and SSRI's can be used. Bone disease should be treated with vitamin D supplementation and bisphosphonates.</p>	
<p><u>Benefit</u></p>	<p>The subject of this NDA, Ocaliva (obeticholic acid) is a modified bile acid and FXR agonist. It is derived from the primary human bile acid, and natural human FXR ligand, chenodeoxycholic acid (CDCA). The primary mechanism of action is based on FXR-mediated activation resulting in release of FGF-19 from the intestine and down-regulation of bile acid synthesis in the liver.</p> <p>FXR activation suppresses cholesterol 7 alpha-hydroxylase, the rate-limiting enzyme in bile acid synthesis from cholesterol. In this way a negative feedback pathway is established in which synthesis of bile acids is inhibited when cellular levels are already high. FXR can be considered as a bile acid sensor that has evolved to maintain the enterohepatic circulation of bile acids and to protect hepatocytes from the toxicity of cellular bile acid overload. Besides the liver, FXR is expressed in the intestine, kidney and adipose tissue.</p> <p>Consistent with its proposed mechanism of action, the applicant demonstrated <i>in vivo</i>, that treatment with Ocaliva resulted in increases in FGF-19 concentration, which was associated with a reduction in C4 (a bile acid precursor) and the endogenous bile acids, CDCA and cholic acid.</p> <p>Efficacy was assessed in one 12-month, double-blind,</p>	<p>Relative to placebo, both Ocaliva treatment groups achieved statistically significant response rates, defined as 12-Month value of ALP < 1.67×ULN, and 12-Month value of TB ≤ ULN (i.e., within normal limits), and ALP reduction from baseline at Month 12 ≥ 15%.</p> <p>In FDA's post-hoc analysis employing cut-points of ALP that, based on a cohort within the Global PBC Study Group, <u>may</u> predict a clinical benefit (transplant-free survival), both Ocaliva treatment groups demonstrated higher response rates than placebo.</p> <p>Overall, the data support that Ocaliva demonstrates an effect of reducing liver-derived ALP in a statistically significant and clinically meaningful group of patients, and that these effects are over and above that which could be achieved with UDCA alone. This added effect is consistent with the mechanism of action of Ocaliva, and it</p>

	<p>placebo-controlled trial in 216 adult subjects with PBC randomized 1:1:1 to placebo, OCA titration (5 mg with option to up-titrate to 10 mg after 6 months, if patient was tolerating the drug but not achieving an adequate response), or OCA 10 mg.</p> <p>The primary efficacy endpoint was a composite of ALP and TB response criteria at month 12. A patient was designated a responder if all 3 of the following conditions were met:</p> <ul style="list-style-type: none"> • 12-Month value of ALP < 1.67×ULN • 12-Month value of TB ≤ ULN • ALP reduction from baseline at Month 12 ≥ 15%. <p>There were no formal secondary endpoints.</p> <p>In the trial, 91% of participants were women, 94% were white, and the mean age was 56 years. Twenty-nine percent of participants were from North America, while 67% were from Europe. Ninety percent of participants were classified as having early stage PBC, by Rotterdam criteria.</p> <p>Both OCA treatment groups showed a superior difference in the proportion of patients achieving response at month 12 when individually compared to placebo. At month 12, 10% of subjects in the placebo arm, 46% of subjects in the OCA titration arm, and 48% of subjects in the OCA 10 mg arm achieved a response.</p> <p>The applicant sought to rely on evidence from the Global PBC Study Group, a large, multi-national retrospective cohort study of UDCA treated and untreated PBC patients across all</p>	<p>is biologically plausible that Ocaliva may attenuate the hepatocellular damage induced by the accumulation of toxic bile acids. Further, it seems plausible, based on data observed with UDCA-induced ALP reductions of this magnitude, that Ocaliva may delay the progression of PBC to cirrhosis, need for liver transplantation, and death.</p> <p>Preliminary evidence supporting the efficacy and safety of Ocaliva as monotherapy was provided.</p> <p>Supportive data were provided by reductions in GGT and IgM with Ocaliva relative to placebo</p> <p>The applicant’s proposal to consider up-titration of dose at 3 months, based on efficacy and tolerability, is adequately supported.</p> <p>Ocaliva is taken once daily and can be taken with or without food.</p>
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stages of the disease, to support that these responder criteria are predictive of clinical benefit (transplant-free survival). However, FDA determined that because patients enrolled in the applicant's pivotal trial were almost exclusively in early stage PBC, the Global PBC Study Group findings could not be relied upon to demonstrate the potential for clinical benefit with Ocaliva. Furthermore, because 92% of enrolled patients had a normal TB at baseline, the trial could not determine an effect of Ocaliva on TB or its contribution to the composite endpoint. The FDA determined that the approval would need to rely solely on ALP, which would need additional support as a stand-alone surrogate endpoint reasonably likely to predict clinical benefit.

To explore the relationship between ALP and clinical benefit, the FDA analyzed data from a cohort of PBC patients (early stage and on concomitant UDCA; n=909) from the Global PBC Study Group. 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 patient PBC cohort. Using those data, FDA statistical reviewers were able to establish ALP cut points that consistently were associated with about 2.5-fold or greater hazard ratio for death and liver transplantation. The stratified cut points developed were:

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×ULN
- ALP reduction from baseline at Month 12 ≥ 40%;

Else if baseline ALP was ≥ 1.67×ULN but < 2.0×ULN, then a patient would be designated as a responder if both of the following conditions were met:

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

FDA statistical reviewers then applied those cut points to a subset of subjects from the Ocaliva pivotal trial – those with TB within normal range and concomitantly receiving UDCA (n=181). Using the FDA’s stratified cut points, 5% of subjects in the placebo arm, 38% of subjects in the OCA titration arm, and 43% of subject in the OCA 10 mg arm achieved a response. Therefore, it was believed that the Ocaliva-induced reductions in ALP, which were over and above those achieved with UDCA alone, may provide a clinical benefit. However, additional levels of evidence were needed to support reliance on ALP as a stand-alone surrogate endpoint reasonably likely to predict clinical benefit in PBC patients, within the context of the Ocaliva NDA:

- Mechanism of action of Ocaliva relative to UDCA
 - UDCA: Alteration of the hydrophobicity index of the endogenous bile acid pool, thus decreasing the intracellular concentration of bile acids and protecting hepatocytes and cholangiocytes against cell death induced by cytotoxic bile acids.
 - Ocaliva: FXR agonism resulting in suppression of bile

	<p>acid synthesis from cholesterol and increased transport of bile acids out of hepatocytes, thus further reducing hepatic exposure to bile acids.</p> <ul style="list-style-type: none">• Biologic plausibility of Ocaliva’s effect on the pathogenesis of PBC<ul style="list-style-type: none">○ Toxic hydrophobic bile acids in the liver tissue contribute to the liver damage in PBC, and modulation of this toxic pool is believed to be beneficial in patients with PBC.• Evidence from Ocaliva clinical trials that Ocaliva does what it is purported to do<ul style="list-style-type: none">○ FGF-19 concentration increased and was associated with a reduction in C4 (a bile acid precursor) and the endogenous bile acids, CDCA and cholic acid, in patients receiving Ocaliva, consistent with FXR agonism.• Clinical trial data on UDCA and reductions in ALP and relationship to clinical benefit<ul style="list-style-type: none">○ UDCA registrational trial data: Incidence of treatment failure (death; need for liver transplantation; histologic progression by 2 stages or to cirrhosis; development of varices, ascites, encephalopathy; doubling of bilirubin; marked worsening of fatigue or pruritus; inability to tolerate the drug; voluntary withdrawal) was 23% in the UDCA treatment arm versus 47% in the placebo arm, and statistically significant reductions from baseline were seen in ALP (and TB). In a supportive trial, the median percent change in ALP in UDCA-treated patients was -42.4% versus +2.8% in placebo-treated patients (and the proportion of patients exhibiting more than a 50% increase in TB was 9.4% and 28.9%, in the UDCA	
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	<p>and placebo groups, respectively). This was associated with a statistically significant reduction in the incidence of duct paucity in UDCA-treated patients relative to placebo-treated patients. In a supportive trial, 28 of 50 (56%) UDCA-treated subjects showed improvement in liver histology over 2 years versus 13 of 45 (29%) placebo-treated subjects, and statistically significant changes from baseline were seen in ALP (and TB).</p> <ul style="list-style-type: none">• Epidemiologic data on UDCA and reductions in ALP and relationship to clinical benefit<ul style="list-style-type: none">○ Global PBC Study Group: ALP response to UDCA at one-year follow-up shows improved transplant-free survival (all stages of PBC pooled).○ UK PBC Study Group: Patients with early-stage PBC who have a biochemical response to UDCA at 1 year show improved survival without adverse outcome, relative to non-responders.○ Other epidemiologic data (Pares 2005; Corpechot 2008; Corpechot 2011) supported that patients with a biochemical response to UDCA at one year had improved transplant-free survival• Natural history of ALP in untreated PBC patients<ul style="list-style-type: none">○ Based on untreated early stage PBC patients within the Global PBC Study group, ALP levels remained elevated over 5 years of follow-up, i.e., they did not spontaneously improve.• Effect of Ocaliva in healthy volunteers<ul style="list-style-type: none">○ In healthy volunteers treated with Ocaliva doses of 5 mg, 10 mg, and 25 mg, no meaningful changes in ALP were observed.	
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	<ul style="list-style-type: none">• Ocaliva exposure-response relationship on ALP in PBC patients<ul style="list-style-type: none">○ An exposure-response relationship of reduction in ALP with total obeticholic acid concentrations was demonstrated, with a plateauing of effect at >40 ng/mL• The durability of the ALP reductions<ul style="list-style-type: none">○ Ocaliva-induced reductions in ALP were maintained through 30 months of follow-up• Determination that ALP reductions reflect liver-derived ALP<ul style="list-style-type: none">○ GGT, also a marker of cholestasis, declined in Ocaliva-treated patients relative to placebo-treated patients• ALP assay performance<ul style="list-style-type: none">○ FDA evaluated the performance of the ALP assay and found it to be adequate; accuracy was within 10%.• Intra-subject variability of ALP as observed in Ocaliva clinical trial populations<ul style="list-style-type: none">○ Mean intra-subject SD variability was similar across Ocaliva and placebo treatment groups; there were similar numbers (percents) of ‘outliers’ among the placebo and treatment arms who contributed to the variability○ Variability in the Ocaliva treatment groups was contributed to by treatment response, concomitant use of BAS, and treatment interruptions, as well as the inherent variability of biomarkers. Variability in the placebo group was contributed to by progression of disease and hepatic insult, as well as the inherent variability of biomarkers.○ Less intra-subject ALP variability occurred in Ocaliva treatment arms during the final 6 months of treatment,	
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when ALP response is more “stabilized”

- Intra-subject variability was higher in the highest tertile of baseline ALP levels compared with the lower two tertiles.

Sub-group analyses were conducted for age (<65 and ≥65). As the vast majority of trial participants were female and white, no meaningful sub-group analyses could be conducted for gender or race. It appeared that more patients under the age of 65 achieved a response in all treatment groups (placebo, OCA titration, OCA 10 mg) relative to those 65 years and older; however, the 65+ age group represented only 18.5% of the ITT population.

Ninety-three percent of participants in the pivotal trial were on concomitant UDCA therapy, while sixteen (7%) participants received OCA as monotherapy. These sixteen subjects were pooled with participants in a phase 2 OCA 10 mg monotherapy trial, who had ALP ≥1.67xULN and/or TB >ULN. In all, 27 participants received placebo monotherapy and 24 participants received OCA 10 mg monotherapy. At month 3, 4% of placebo-treated subjects versus 38% of OCA 10 mg-treated subjects achieved a response according to the applicant’s primary efficacy responder definition. This compares favorably with the results in the combination therapy sub-group, where 5% of placebo+UDCA-treated subjects versus 41% of OCA 10 mg+UDCA-treated subjects achieved a response.

In exploratory analyses, GGT was reduced in Ocaliva treated

	<p>patients relative to placebo, as was IgM.</p> <p>Patients in the phase 3 trial were considered for up-titration at 6 months, although clinical data demonstrated that, at the population level, the trend of reduction in ALP saturated at 3 months with 5 mg once daily dosing and there was minimal further decrease in ALP from month 3 to month 6 and beyond with the same dose.</p> <p>Ocaliva is taken once daily and can be taken with or without food.</p>	
<p><u>Risk</u></p>	<p>The safety of Ocaliva was assessed in 432 patients with PBC, including 290 who were treated with Ocaliva for at least 6 months, 232 who were treated for at least 12 months, and 70 who were treated for at least 2 years. Doses ranged from 5 mg to 50 mg once daily, with 131 patients receiving Ocaliva 10 mg once daily and 70 receiving Ocaliva 5 mg once daily. Eighty-five percent of subjects across the two phase 2 and one phase 3 trials were receiving concomitant UDCA.</p> <p>The most common adverse reactions reported with Ocaliva treatment, that were dose dependent and occurred with greater frequency than with placebo treatment were pruritus, fatigue, arthralgia, and oropharyngeal pain. Of patients who developed pruritus, 30 of 59 (59%) in the Ocaliva 10 mg arm, 24 of 39 (62%) in the Ocaliva titration arm, and 14 of 28 (50%) in the placebo arm required interventions to treat the pruritus (e.g., bile acid sequestrant or anti-histamine, dosage adjustment, or treatment</p>	<p>Ocaliva is contraindicated in patients with complete biliary obstruction.</p> <p>Dose-dependent clinically significant liver-related adverse reactions can occur. These occur more frequently at doses exceeding the maximum recommended dose of 10 mg.</p> <p>Pruritus, which may be severe, and fatigue were the most common treatment-emergent adverse reactions.</p> <p>Treatment with Ocaliva is associated with dose-dependent reductions in HDL-C.</p> <p>Higher systemic exposures to</p>

	<p>interruption.)</p> <p>Bile acids are contraindicated in complete bile obstruction as the obstruction to bile flow would result in accumulation of bile acids which would further damage the bile ducts.</p> <p>Clinically significant liver-related adverse reactions, including abnormal liver biochemical tests, ascites, jaundice, portal hypertension, and PBC flare were dose dependent and occurred more frequently at doses exceeding the maximum recommended dose of 10 mg.</p> <p>Severe pruritus occurred in 23% of patients in the Ocaliva 10 mg arm, 19% of patients in the Ocaliva titration arm, and 7% of patients in the placebo arm.</p> <p>Dose dependent reductions in HDL-C levels of 19% and 12% occurred in the Ocaliva 10 mg treatment arm and Ocaliva titration arm, respectively, compared to a 2% reduction in the placebo arm.</p> <p>The systemic exposure ($AUC_{0-9 \text{ days}}$) 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.</p> <p>Bile acid binding resins may reduce the absorption, systemic exposure and efficacy of Ocaliva.</p> <p>Concomitant administration of 25 mg warfarin as a single</p>	<p>obeticholic acid are observed in patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment .</p> <p>Absorption of Ocaliva is impaired by co-administration with a bile acid binding resin.</p> <p>INR is decreased when Ocaliva and warfarin are co-administered.</p> <p>Ocaliva may increase the exposures of drugs that are CYP1A2 substrates.</p> <p>Ocaliva may increase the exposures of drugs that are CYP2C19 substrates.</p> <p>In 2-year oral carcinogenicity studies in rats, there were treatment-related benign granular cell tumors in the cervix and vagina of female rats at a dose approximately 12 times the human exposure at the MRHD.</p>
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	<p>dose with Ocaliva 10 mg once daily resulted in a 13% increase in systemic exposure to S-warfarin and an 11% decrease in maximum International Normalized Ratio (INR).</p> <p>Concomitant administration of 200 mg caffeine (a CYP1A2 substrate) with Ocaliva 10 mg once daily resulted in a 42% increase in AUC of caffeine, and 6% increase in C_{max}.</p> <p>Concomitant administration of 20 mg omeprazole (a CYP2C19 substrate) as a single dose with Ocaliva 100 mg once daily resulted in a 32% increase in AUC and a 33% increase in C_{max} of omeprazole.</p> <p>In 2-year oral carcinogenicity studies in mice, there were no treatment-related neoplastic findings in male or female mice. In 2-year oral carcinogenicity studies in rats, there were treatment-related benign granular cell tumors in the cervix and vagina of female rats at a dose approximately 12 times the human exposure at the MRHD; there were no treatment-related neoplastic findings in male rats.</p>	
<p><u>Risk Management</u></p>	<ol style="list-style-type: none"> 1. Use in patients with complete biliary obstruction 2. Serious liver-related adverse reactions 3. Pruritus 4. Reduction in HDL-C 5. Concomitant use of a bile acid binding resin 6. Concomitant use of warfarin 7. Concomitant use with CYP1A2 substrates 8. Use in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C) 	<ol style="list-style-type: none"> 1. Ocaliva is contraindicated in patients with complete biliary obstruction. 2. HCPs should not prescribe doses of Ocaliva in excess of the maximum recommended dose of 10 mg. All patients should be monitored for alterations in liver biochemical tests and development of liver-related adverse reactions.

		<ol style="list-style-type: none">3. The incidence and severity of pruritus may be attenuated by adding bile acid sequestrants or anti-histamines; reducing the dosage of Ocaliva, or temporarily interrupting treatment with Ocaliva for up to 2 weeks followed by restarting at a reduced dosage.4. Monitor serum lipid levels. In patients who do not respond to Ocaliva after 1 year at the highest recommended dosage that can be tolerated, and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.5. If a patient is taking a bile acid binding resin, Ocaliva should be taken at least 4 hours before or after taking the bile acid binding resin.6. Monitor INR and adjust the dose of warfarin, if needed, to maintain the target INR range when co-administering Ocaliva and warfarin.7. Monitor drug concentrations of CYP1A2 substrates with a narrow therapeutic index when co-administering with Ocaliva.8. In patients with moderate to severe
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		<p>hepatic impairment, initiate Ocaliva at 5 mg once weekly. At 3 months, if the patient is tolerating Ocaliva but has not had an adequate response, titrate to 5 mg twice weekly. If, after 3 months on the 5 mg twice weekly regimen, the patient is tolerating Ocaliva but has not had an adequate response, titrate to 10 mg twice weekly.</p> <p>The sponsor has agreed to a PMC to develop a lower strength tablet to facilitate dosing in this population.</p> <p>There are no serious safety concerns that warrant the need for a REMS.</p>
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Other Background

Regulatory History

In January 2006, IND 63307 was opened for obeticholic acid for the treatment of PBC.

In February 2007, an End-of-Phase 1 meeting was held. The applicant proposed the use of alkaline phosphatase (ALP) as a surrogate primary endpoint for phase 2 and 3 trials. FDA expressed concern regarding the use of ALP as a primary endpoint.

In April 2008, obeticholic acid for the treatment of PBC was granted orphan drug designation.

In August 2010, an End-of-Phase 2 meeting was held. The applicant proposed using ALP as a surrogate endpoint in the phase 3 trial. FDA did not agree that ALP alone would be considered an appropriate endpoint to establish efficacy in the treatment of PBC, but that the onus was on the applicant to provide convincing evidence that a proposed surrogate endpoint would be reasonably likely to predict clinical benefit.

In February 2011, a Type A meeting was held. The purpose of the meeting was to discuss the acceptability of ALP-based endpoints to support NDA approval. No agreement was reached at the meeting.

In October 2011, a Type A meeting was held to further discuss the phase 3 trial design. FDA remained concerned regarding the considerable variability in the performance of biomarkers in predicting long term outcomes in patients with PBC. Subsequent to this meeting, FDA agreed with the applicant's plan to evaluate data across multiple studies to better understand the relationship between biochemical markers and clinical outcomes in PBC.

In May 2014, Fast Track designation was granted.

A pre-NDA meeting was held in November 2014. Also in November 2014, a rolling review was granted.

The NDA was submitted on June 29, 2015, and granted priority review. A major amendment submitted October 27, 2015 triggered an extension of the PDUFA goal date to May 29, 2016.

Product Quality

There are no product quality issues that preclude approval.

ONDP granted the applicant's claim for Categorical Exclusion for the Environmental Assessment. Additionally, there was no evidence that OCA has endocrine activity.

ONDP concluded that the proposed dissolution test and acceptance criterion are satisfactory. Clinical batches were properly bridged to commercial batches and the biowaiver request for the 5 mg OCA tablets was deemed acceptable.

The Office of Process and Facilities' made a final overall manufacturing inspection "approval" recommendation for the facilities involved in this application.

The Division of Pharmaceutical Analysis (DPA) conducted methods verification and determined that methods were acceptable for quality control and regulatory purposes.

OPQ concluded that based on the stability data submitted, a 24-month expiration dating period is well justified when stored in the proposed container closure system at 25°C.

Non-clinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude approval.

In repeat-dose oral toxicity studies in rodents and non-rodents, the hepatobiliary system was identified as the primary target system of toxicity. Additional primary target organs were the large intestine and bone marrow.

In an oral fertility and early embryonic development study in rats, OCA did not alter male or female fertility or early embryonic development at any dose up to ~13 times the human exposure at the MRHD.

In an embryofetal development study in rats, decreased fetal body weights and increased number of early or late resorptions and nonviable fetuses were observed at doses approximately 40 times the human exposure at the MRHD. In maternal animals, mortality, fetal loss, decreased body weight and food consumption, and decreased body weight gain were observed at doses approximately 40 times the human exposure at the MRHD. In embryofetal development studies in rabbits, there was no evidence of teratogenicity or fetal harm.

In a pre- and post-natal development study in rats, OCA did not produce effects on pregnancy, parturition or postnatal development at doses up to approximately 21 times the human exposure at the MRHD.

In vitro studies showed that OCA at concentrations $\leq 82.8 \mu\text{M}$ had no clear effect on cloned hERG channel currents in HEK293 cells. *In vivo* studies to assess the potential of OCA to affect the cardiovascular system were conducted in telemeterized beagle dogs, with no effects on the cardiovascular system at the highest dose tested (20 mg/kg).

Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

Following oral administration of multiple oral doses of OCA 10 mg once daily, peak plasma concentrations of OCA were achieved at a median time of approximately 1.5 hours; peak plasma concentrations for the conjugates, glyco-OCA and tauro-OCA, were achieved at a median time of approximately 10 hours. Food does not alter the extent of absorption of OCA.

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-fold and ~12-fold, respectively) compared to the parent drug. About 87% of the dose is excreted in feces through biliary secretion, with less than 3% excreted in the urine. For the parent drug, the effective half-life is 24 hours. For the active conjugates, their half-lives have not been well estimated due to extensive enterohepatic recirculation. OCA steady-state is reached in ~5 days.

QT prolongation potential. Obeticholic acid, at doses up to 7.2 times higher than the C_{max} for the 10 mg dose, did not result in significant QTc prolongation. The largest upper bound of the 2-sided 95% CI for the mean difference between obeticholic acid and placebo was below 10 ms.

Effect of age. Based on population PK analyses, age had no impact on the PK of OCA.

Renal impairment. Based on population pharmacokinetic (PK) analyses, renal function (eGFR) was not a significant covariate for OCA clearance/exposure for patients with renal impairment (eGFR from 52 to 433 mL/min/1.73 m²).

Clinical/Statistical – Efficacy

The table below provides a summary of the primary efficacy results from the pivotal trial.

Table 1: Percentage of Adult Patients with PBC Achieving the Primary Composite Endpoint at Month 12 in Trial 1 by Treatment Arm with or without UDCA

	OCALIVA 10 mg (N = 73)	OCALIVA Titration (N = 70)	Placebo (N = 73)
Primary Composite Endpoint			
Responder rate, (%) [95% CI]	48 [36, 60]	46 [34, 58]	10 [4, 19]
Components of Primary Endpoint			
ALP less than 1.67-times ULN, n (%)	40 (55)	33 (47)	12 (16)
Decrease in ALP of at least 15%, n (%)	57 (78)	54 (77)	21 (29)
Total bilirubin less than or equal to ULN, n (%)	60 (82)	62 (89)	57 (78)

*Adapted from FDA statistical reviewer's table

The Office of Scientific Investigations (OSI) conducted inspections of six clinical investigator sites and the applicant site. OSI concluded that “The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.”

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion, and arranged for an inspection of the clinical portion, of a pharmacokinetic study. OSIS concluded that the clinical and analytical data from the audited study were reliable, and could be accepted for further Agency review.

Advisory Committee

A meeting of the Gastrointestinal Drugs Advisory Committee was convened on April 7, 2016. The committee was asked to discuss the following:

- **Discuss whether the evidence from the Global PBC Study Group data presented today on the reduction in alkaline phosphatase (ALP) supports the use of alkaline phosphatase as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage Primary Biliary Cirrhosis (PBC). Comment on the strength of evidence that supports the stratified responder criteria that were developed by the FDA statistical team’s review of the Global PBC Study Group data.**

In general, the committee members agreed that ALP is a reasonable surrogate endpoint in early stage disease, while acknowledging that in more advanced stages of the disease, a different outcome measure would likely be needed, specifically one that incorporated TB.

- **Discuss the appropriateness of the Applicant’s proposed dosage schema, i.e., a starting dose of 5 mg of obeticholic acid (OCA) with up titration to 10 mg after 3 months. Include in your discussion and dosing recommendation the safety and tolerability of obeticholic acid in addition to the biochemical response (alkaline phosphatase reduction).**

In general, there was no disagreement expressed by the committee members. Suggestions were made to follow HDL-cholesterol levels in the phase 4 confirmatory trial, and to attempt to better characterize hepatic-related adverse events, especially in subjects with more advanced stages of PBC, in the phase 4 trial.

- **Discuss the adequacy of the data to support the use of OCA as monotherapy for patients intolerant to ursodeoxycholic acid (UDCA). Include in your discussion whether the applicant should be required to further study the use of OCA as monotherapy.**

In general, the committee members believed there was sufficient information on OCA monotherapy, but also supported further study of OCA monotherapy in patients who are non-responders to UDCA, or intolerant of UDCA.

- **Discuss the adequacy of the data to support the use of OCA in moderately advanced and advanced stages of PBC. Include in your discussion whether the applicant should be required to further study the use of OCA in moderately advanced and advanced stages of PBC.**

The committee members acknowledged that there were no data on patients with advanced disease, and the data on patients with moderately advanced disease were insufficient to draw any conclusion regarding efficacy or safety. The committee members supported further study of OCA in patients with moderately advanced and advanced stages of PBC.

- **Discuss whether the available evidence (i.e., PK modeling, dose response) supports the FDA’s proposed dosing of OCA in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis.**

The committee members concluded that there were insufficient data from which to draw any conclusions on the use of OCA in patients with moderately advanced and advanced cirrhosis; however, some members opined that patients with compensated cirrhosis, in general, tolerate drugs well, but patients with decompensated cirrhosis do not.

- **Discuss the pros and cons of continuing OCA treatment in patients who do not demonstrate reduction in alkaline phosphatase after 6 months of treatment on a maximally tolerated dose. Take into consideration the risk of alterations in lipid profile vs. the potential for benefit.**

Some committee members thought that “stopping rules” may be premature, and that there could be potential benefits of OCA that are not captured in ALP. One member opined that one should not count on “hope of benefit” with continued therapy and believed that patients should be given a 12-month trial of OCA, and if no biochemical response was achieved, the drug should be discontinued.

- **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 committee voted 17 Yes, and 0 No. Committee members cited the absence of a clear safety signal, the ‘effect’ observed, the rarity of the condition, and the unmet medical need. Committee members reiterated their belief that the applicant needs to provide more data on the long-term safety of OCA, and the safety and efficacy of OCA in cirrhotic patients, and in patients with moderately advanced disease.

- **Discuss what if any changes in the enrollment criteria or design of the postmarketing confirmatory trial would be necessary to obtain any additional information that you think is necessary for full/regular approval of OCA for the treatment of PBC.**

Alternatively, discuss what additional post-marketing studies you think would be necessary to obtain any data or information that has not been provided.

Recommendations included:

- *Do not allow use of an historical control comparator.*
- *Obtain additional data on the use of OCA as monotherapy.*
- *Look at biochemical criteria and PK, especially in more advanced stage disease patients.*
- *Continue accrual beyond 2 years.*
- *Collect data on cardiovascular adverse events.*
- *Don't exclude compensated cirrhotics, rather stratify them and look at delay to decompensation.*
- *Obtain more data on OCA in patients with more advanced stages of the disease.*

There were 3 speakers during the Open Public Hearing portion of the meeting. All three supported approval of the product, citing the need for alternative treatment options.

Medical Policy Council (MPC)

On April 13 and May 13, 2016, DGIEP presented data supporting its belief that the NDA for Ocaliva could rely on ALP as a surrogate endpoint reasonably likely to predict clinical benefit under an accelerated approval pathway. The MPC concurred with DGIEP's recommendation.

Pregnancy Considerations

Consistent with the Pregnancy and Lactation Labeling Rule guidelines, The **Use in Specific Populations** section, **Pregnancy** subsection, of the product label will state that the available human data on the use of Ocaliva during pregnancy are limited and insufficient to inform a drug-associated risk.

In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13 times and 6 times human exposures, respectively, at the MRHD of 10 mg. Obeticholic acid administered to rabbits at doses up to 20 mg/kg/day (approximately 6 times the human exposure at the MRHD) was not teratogenic.

There is no information on the presence of obeticholic acid in human milk, the effects on the breast fed infant or the effects on milk production.

Pediatrics

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Ocaliva have not been established in pediatric patients.

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

Other Relevant Regulatory Issues

Tradename Review

The applicant's proposed tradename "Ocaliva" is acceptable from both a safety and misbranding perspective. The applicant was informed of this determination on October 27, 2015.

Consults

Division of Biometrics VI (DB VI)

OPQ consulted DB VI to evaluate the stability of obeticholic acid drug substance under long-term conditions of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. DB VI concluded that the stability support the proposed shelf life of 24 months for drug substance under the long-term conditions of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

Division of Bone Reproductive and Urologic Products (DBRUP)

DBRUP was consulted to provide their opinion and expertise in the evaluation of the results of the DEXA scan performed in subjects in the phase 3 trial; a determination of the significance of a numerically higher rate of fractures observed in Ocaliva-treated subjects relative to placebo-treated subjects in the same trial; and recommendations for further investigations and evaluations for follow-up if fractures are determined to be a potential adverse event signal.

DBRUP concluded that:

- Mean changes in lumbar and femoral neck bone mineral density over 12 months appear comparable across the 3 treatment groups. Generally, mild reductions in BMD were observed in all treatment groups. These BMD changes are unlikely to be associated with increased fracture risk. Overall, the incidence of osteoporosis in the OCA trial is low compared to that reported in previous PBC studies.
- Discounting one subject in the OCA 10 mg group who sustained a sternal fracture before dosing, 3.4% of subjects treated with OCA had fractures, as did 4% of placebo-treated subjects. These rates are consistent with background fracture rates documented in the age and sex-matched general population. There were 5 fragility fractures in 4 subjects out of

8 subjects with fractures. The other fractures were most likely traumatic in origin. This fracture incidence (4%) is less than reported historically with PBC.

- No clear association between BMD changes and fracture risk can be shown with the sparse data. The changes are comparable to the means of all subjects in the 3 treatment groups, and therefore to the means of the age-related general population.

The DXA and fracture data provided do not indicate a bone safety issue with Ocaliva.

Clinical Outcome Assessment (COA)

COA was consulted to review the applicant's three patient reported outcome (PRO) instruments that were used to assess pruritus severity and impact (Itch domain of the PBC 40, which assesses impact of itching; 5-D Pruritus Scale, total score assesses severity and impact of itching; Pruritus Visual Analog Scale). These instruments were considered part of the safety assessment of obeticholic acid. COA staff concluded that the "instruments appear fit-for purpose for this drug development program. However, it is unclear what threshold of change represents clinically meaningful deterioration on each of these scales."

Office of Prescription Drug Promotion (OPDP)

OPDP reviewed the draft package insert (PI) for Ocaliva. OPDP provided suggestions to improve the clarity of the PI, as well as to remove potentially promotional language.

Division of Medication Error, Prevention, and Analysis (DMEPA)

DMEPA was consulted to review the proposed prescribing information and carton labels for possible sources of medication errors. DMEPA recommended changes to the container label, including revising the product code in the NDC numbers, reorienting the barcode to improve readability, increasing the prominence of the established name, and decreasing the prominence of the company name on the principal display panel.

Division of Pediatric and Maternal Health

The Division of Pediatric and Maternal Health (DPMH) was consulted to provide assistance applying the Pregnancy and Lactation Labeling Rule (PLLR) requirements to the Ocaliva labeling. There have been no studies with Ocaliva in pregnant women. A review of the published literature revealed no data on obeticholic acid use in pregnancy or lactation, or effects on fertility and/or reproduction. A search of the applicant's pharmacovigilance database found one case of pregnancy in a patient treated with obeticholic acid in a clinical trial. The subject experienced a spontaneous abortion approximately 26 days after obeticholic acid was discontinued. Because PBC disproportionately affects females versus males (approximately 10:1) and is typically diagnosed in patients with a mean age of 40 to 60 years, this suggests that females of

reproductive potential may be exposed to Ocaliva during pregnancy. For this reason, DPMH has recommended that more data be collected postmarketing in this group of female patients, either in a pregnancy monitoring study or a substudy within a patient registry.

DPMH also noted that there are no studies that have been conducted to determine whether obeticholic acid is present in human milk, nor have studies been conducted in regards to the effects of obeticholic acid on the breast-fed infant or its effects on milk production. Because Ocaliva's predominant distribution is in the enterohepatic circulation, the maternal plasma concentration is expected to be low, thus only a small amount of Ocaliva may transfer to the breastfed infant.

Finally, there are no human data available regarding the effects of Ocaliva on fertility. No effects of obeticholic acid on fertility, mating or male reproduction were observed in rats at exposure multiples up to 15 times human exposure at the MRHD.

DPMH restructured the Ocaliva label to be consistent with the PLLR guidelines.

Risk Evaluation and Mitigation Strategies (REMS)

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology provided a consultative review to determine if a risk evaluation and mitigation strategy (REMS) is needed for Ocaliva (obeticholic acid), a new molecular entity. DRISK concluded that "the benefit-risk profile for obeticholic acid is acceptable and the risks will be communicated to the prescribing community through the labeling."

Postmarketing Requirements and Commitments

Post Marketing Requirements

- 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).

- 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).

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.

(b) (4)

Post Marketing Commitments

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.

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/s/

AMY G EGAN
05/27/2016