ADVISORY COMMITTEE BRIEFING DOCUMENT
GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Meeting Date: 13 September 2024

Supplemental New Drug Application for Obeticholic Acid (OCA) for the Treatment of Patients with Primary Biliary Cholangitis (PBC) in Combination with Ursodeoxycholic Acid (UDCA) in Adults with An Inadequate Response to UDCA, or as a Monotherapy in Adults Unable to Tolerate UDCA
(New Drug Application [NDA] 207999)

Sponsor:

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ADVISORY COMMITTEE BRIEFING MATERIALS:
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this report.

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	Anti-mitochondrial antibodies
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
AUC_{0-24h}	area under the plasma concentration time curve from 0 to 24 hours
CCI	Charlson Comorbidity Index
CI	confidence interval
COVID	coronavirus-19
CP	Child Pugh
CP-B	Child-Pugh Class B cirrhosis
CP-C	Child-Pugh Class C cirrhosis
CV	cardiovascular
DAG	directed acyclical graph
DB	double-blind
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EAIR	exposure-adjusted incidence rate
EC	external control
eDISH	evaluation of drug-induced serious hepatotoxicity
EHR	electronic health record
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
FIB-4	fibrosis-4
FXR	farnesoid X receptor
GGT	gamma-glutamyl transferase
HDL	high-density lipoprotein
HR	hazard ratio
HSAC	Hepatic Safety Adjudication Committee

Abbreviation	Definition
HOC	Hepatic Outcomes Committee
IPCW	inverse probability of censoring weighting
ITT	intent to treat
LDL	low-density lipoprotein
LTSE	long-term safety extension
MACE	Major Adverse Cardiovascular Events
MASH	metabolic dysfunction-associated steatohepatitis
MELD	Model End-Stage Liver Disease
MOA	mechanism of action
NDA	new drug application
OCA	obeticholic acid
PBC	primary biliary cholangitis
PK	pharmacokinetic
PMR	postmarketing requirement
PPAR	peroxisome proliferator-activated receptor
PY	patient-years
RCT	randomized controlled trial
RWD	real-world data
RWE	real-world evidence
SAE	serious adverse event
SMR	standardized mortality/morbidity ratio
TEAE	treatment-emergent adverse event
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit normal
US	United States
USPI	United States Prescribing Information
WADD	weighted average daily dose

EXECUTIVE OVERVIEW

Ocaliva® (obeticholic acid; OCA) received accelerated approval for primary biliary cholangitis (PBC) in the United States (US) in May 2016, as the first second-line treatment for adult patients with PBC for use either in combination with ursodeoxycholic acid (UDCA) in patients with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA. Ocaliva was granted accelerated approval based on a reduction in ALP, a marker of cholestasis and recognized as the primary reliable marker for PBC clinical outcomes.

Intercept Pharmaceuticals, Inc., a wholly-owned subsidiary of Alfasigma S.p.A, (Intercept) is seeking conversion of Ocaliva from accelerated to standard approval. Standard approval is contingent on confirming benefit on clinical outcomes such as hepatic decompensation, liver transplant, and death. There is no change proposed to the currently indicated population (i.e., patients with PBC without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension).

PBC is a serious rare disease with an unmet need for second-line therapies targeting multiple mechanisms of action.

PBC is a chronic, progressive disease, which injures, inflames, and ultimately destroys the bile ducts in the liver, causing bile to build up in and damage the liver. There is no cure. As the disease progresses, patients may experience jaundice, abdominal pain, swelling of the spleen, osteoporosis, reduced immunity, gastrointestinal bleeding, occasional mental confusion, and bone, muscle, or joint pain, among other symptoms (Mayo Clinic 2023, Cleveland Clinic 2023). Without treatment, the disease can result in irreversible hepatic decompensation, liver transplant, and ultimately death. PBC is a rare disease that primarily affects women between the ages of 40 and 60 (Trivella 2023) and has a total US patient prevalence of approximately 105,000 (Buchanan-Peart 2023).

The available first-line treatment for PBC is UDCA; however, approximately 40% of PBC patients have an inadequate response to UDCA, and another 5% of patients are intolerant of UDCA (Invernizzi 2017). The Food and Drug Administration (FDA) recently granted accelerated approval to a second-line treatment, IQIRVO (elafibranor). This therapy and seladelpar, an additional product in development, are peroxisome proliferator-activated receptor (PPAR) agonists and have a distinct mechanism of action (MOA) from Ocaliva, which is a farnesoid X receptor (FXR) agonist. Both UDCA and PPAR agonists target cholestasis and inflammation. As explained in greater detail below, Ocaliva, in contrast, targets fibrosis, in addition to cholestasis and inflammation. Ocaliva therefore retains a distinct and necessary role in the treatment of PBC that complements the activity of other PBC therapies. Moreover, emerging evidence suggests that a combination of these therapies may present the best therapeutic outcomes for patients.

FDA considers the totality of evidence when evaluating the safety and effectiveness of drugs and the totality of evidence for Ocaliva demonstrates a positive benefit-risk profile in the currently indicated population.

FDA uses a totality of evidence approach when considering the quantity and quality of evidence to support effectiveness for drugs and biological products (US FDA 1998, Sherman 2017). The totality of evidence for Ocaliva continues to demonstrate a positive benefit-risk profile for

patients with PBC who are at high risk for disease progression within the current indicated population. As further detailed below, this evidence includes the pivotal trial Study 301, the 301 long-term safety extension (LTSE), an adequate and well-controlled real-world evidence (RWE) Study 405, Study 302, and other supporting RWE studies.

Study 301, conducted for approval of Ocaliva, demonstrated a clinically and statistically significant rapid and sustained reductions of ALP levels up to 5 years. This reduction was not only observed in the Ocaliva-treated patients in the double-blind (DB) phase, but also patients who were initially randomized to placebo during the DB phase and later transitioned to Ocaliva during the LTSE. Clinically significant reductions were also observed in other serum markers, such as cholestasis (GGT) and hepatocellular injury (ALT and AST).

The availability of commercial Ocaliva for over 8 years has provided an opportunity to assess the benefit-risk profile of the drug using real-world data (RWD) (e.g., registry and claims databases) across multiple studies. Study 405, an adequate and well-controlled RWE study, verifies the clinical benefit and safety profile of Ocaliva. The protocol and analyses for Study 405 were pre-specified and align to FDA RWE guidances. This observational, retrospective study compared Ocaliva-treated patients to matched non-Ocaliva-treated patients from the US Komodo Healthcare Map™ database (referred to as Komodo database). Study 405 closely aligns to the current indicated patient population and had a primary endpoint of time to the first event of the composite endpoint of all-cause death, liver transplant, or hospitalization for hepatic decompensation, whichever occurred first. Study 405 demonstrated a statistically and clinically meaningful treatment benefit of event-free and transplant-free survival while supporting the known safety profile of Ocaliva. In addition to Study 405, multiple additional supportive RWE studies across a number of geographies that have been conducted and are discussed herein provide further evidence of the favorable benefit-risk profile for Ocaliva.

Study 302, the designated confirmatory study, could not be completed due to patient recruitment and retention challenges, and these challenges were associated with multiple forms of bias in the pre-specified intent-to-treat (ITT) analysis, including treatment crossover. This emphasizes the difficulty in undertaking placebo-controlled randomized trials for any product in a rare and slowly progressive disease with a well-established and easily measurable biomarker in the presence of a commercially available, disease-modifying therapy (Jones 2024).

Despite this, resulting data when employing post-hoc analyses to adjust for some of the observed biases shows trend towards a clinically meaningful benefit for Ocaliva for the primary outcome event.

Taken together, these multiple sources of evidence across differing populations, geographies, and varying methodologies demonstrate the clinically meaningful impact of Ocaliva on the long-term outcomes of patients with PBC. In addition, Intercept is committed to undertake additional studies based on the availability of robust postmarketing data to further study the clinical benefit of Ocaliva for patients living with PBC.

Ocaliva has a well-characterized, manageable safety profile.

The safety profile of Ocaliva is well characterized and manageable under the care of specialists, as shown in the clinical studies, RWE, and more than 8 years (more than 42,000 patient-years [PYs]) of cumulative postmarketing experience. The clinical trial program, including RWE, did

not find evidence for excess risk of cardiovascular (CV) events, dyslipidemia, gallbladder/ gallstone, and renal adverse events (AEs). The most common AE was pruritus (itchy skin), which does not correlate with more advanced PBC disease stage or with clinical safety outcomes and was generally mild to moderate in severity and manageable with drug interruption or medication. Further, for patients within the indicated population, the risk for liver injury is low. As detailed below, in May 2021, the United States Prescribing Information (USPI) was updated to contraindicate patients with a prior decompensation event or compensated cirrhosis who have evidence of portal hypertension, and since that label change, the cumulative postmarketing experience shows a significant decrease in risk for serious hepatic events with no new safety signals.

In addition, the risks that are associated with use of Ocaliva can be adequately and effectively managed. Ocaliva is generally prescribed by hepatology and gastroenterology specialists who are well-versed in use of Ocaliva for PBC and closely monitor their patients while on therapy. Further, Ocaliva is generally made available through a small network of specialty pharmacies and payors that require prior authorization (labs, attestation, and re-authorization). All prior authorization requests require submission of labs in addition to the prescriber's attestation that there are no contraindications and periodic re-authorization is required. Finally, a majority of patients who are prescribed Ocaliva enroll in Interconnect® Support Services, an Intercept patient support program that requires healthcare providers attest that patients who are prescribed Ocaliva are not contraindicated.

Ocaliva was previously studied for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) (previously called nonalcoholic steatohepatitis [NASH]). There are key differences in the safety profile for Ocaliva for PBC compared to use of Ocaliva for MASH. Not only is PBC a distinct disease from MASH, but the dose of Ocaliva for treatment of PBC is substantially lower (5 mg or 10 mg once daily) than the Ocaliva dose studied for MASH. The recommended starting dose for PBC is 5 mg once daily, in contrast to the studied dose of 25 mg once daily for MASH. Moreover, it is also worth remembering that PBC is a rare cholestatic disease with US prevalence of approximately 105,000 adults. And of the 105,000 patients, approximately 30,000 patients with PBC in the US are eligible for Ocaliva treatment based on the approved USPI (which excludes patients with hepatic decompensation and portal hypertension in the presence of cirrhosis). In contrast, MASH is a disease with background metabolic disorder and US prevalence of 26 million adults. The lower dose and narrower indication at issue here—in addition to the careful management of patients with PBC by specialist practitioners and pharmacies—presents a distinct and well-managed benefit-risk analysis.

FDA regulatory framework allows for flexibility to grant full approval and to maintain accelerated approval even where a confirmatory trial does not succeed—and FDA has exercised this authority in analogous circumstances.

Intercept filed a supplemental NDA (sNDA) on 15 Dec 2023, requesting full approval of Ocaliva for the current indication, based upon a totality of the evidence showing Ocaliva's demonstrated effect on ALP and other biomarkers as well as clinical outcomes. Under the Federal Food, Drug, and Cosmetic Act (FDCA), FDA has considerable discretion to approve drugs through accelerated approval and, once approved, to keep such drugs on the market and to convert such approvals to full approval—even where the designated confirmatory trial fails to meet its

primary endpoint [21 U.S.C. § 356(c)(1), (3)(A)]. For example, ZEPZELCA (lurbinectedin), which was granted accelerated approval in 2020 as a second-line treatment for small-cell lung cancer, was permitted to remain on the market despite the failure of the drug's confirmatory trial to meet its primary endpoint (Liu 2022). There, FDA agreed to additional confirmatory trials and observed that *"[w]hen a confirmatory trial does not meet its endpoint, it does not necessarily mean that the drug is not effective for the indication approved through accelerated approval"*[1] (Liu 2022). More recently, in June 2024, ELEVIDYS (delandistrogene moxeparvovec-rokl) was converted from accelerated to full approval even though its confirmatory trial *"failed to meet its statistical primary endpoint."*[2] In his Center Director Decision Memo, Dr. Peter Marks explained "*In areas of high unmet medical need, FDA has taken the approach of carefully considering the totality of the evidence to determine whether a product could receive approval*."[2]

FDA has taken the position that a flexible, patient-focused approach is particularly appropriate in the rare disease context, where clinical trials typically result in "a lot more residual uncertainty," and where there remains unmet medical need (Karlin-Smith 2024, US FDA 2019). Moreover, the Agency has increasingly looked to RWE in its approval decisions, consistent with the 21st Century Cures Act [21 U.S.C. § 355g(1)] and the Agency's Framework for its RWE program (US FDA 2018a). Taken together, these factors have led FDA to take a weight of the evidence approach to evaluating the ongoing study of drugs approved pursuant to accelerated approval, with careful attention to factors that may affect the outcome of a confirmatory study, as well as additional available supportive safety and efficacy data. FDA has particularly relied upon non-traditional study designs, such as RWE, for rare diseases where a randomized controlled trial (RCT) is *"not ethical or feasible"* (US FDA 2019).

The benefit-risk of Ocaliva is positive for patients with PBC who are at high risk for disease progression (i.e., already failed first-line therapy for PBC) and are within the current USPI indicated population.

This briefing document is organized as follows:

[1] A letter from Patrizia Cavazzoni, Dkt. No. FDA-2021-P-0268 (Oct. 24, 2022), https://www.regulations.gov/document/FDA-2021-P-0268-0005
[2] Center Director Decisional Memo from Peter Marks, Director, CBER, FDA re: BLA 125781/Amendment 34 at 3 (last visited July 29, 2024), *available at* https://www.fda.gov/media/179485/download?attachment.

1. BACKGROUND ON PBC

1.1. Primary Biliary Cholangitis

PBC is a rare, serious, and progressive liver disease with a US prevalence of 105,000 adults (Buchanan-Peart 2023). Without intervention, 25% of patients will progress to liver failure within 10 years (EASL 2017). Cholestasis, inflammation, and fibrosis drive underlying disease activity. Elevations in ALP and other liver biochemistries are reflective of the underlying hepatic disease pathology in patients with PBC. Pruritus and fatigue are the most common symptoms of PBC.

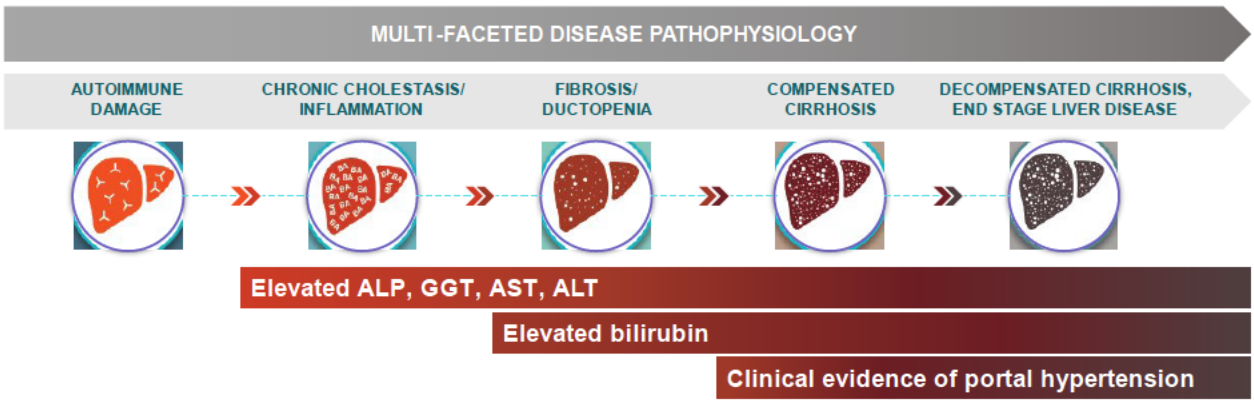
PBC is a rare, serious, life-threatening, cholestatic liver disease with a high unmet need for second-line therapies and prevalence of 105,000 adults in the US (Buchanan-Peart 2023). PBC primarily affects women between the ages of 40 and 60 (Trivella 2023).

PBC is characterized by cholestasis caused by autoimmune destruction of bile ducts with progressive impairment of bile flow in the liver (Murillo Perez 2020). This results in increased hepatocellular bile acid concentrations, which are toxic to the liver. Cholestasis, inflammation and fibrosis drive underlying disease activity. With more advanced disease, and the progressive development of a secondary biliary cirrhosis, hepatic excretory function starts to decline, leading to hyperbilirubinemia and progressive changes in portal hemodynamics ultimately resulting in clinically evident portal hypertension. The greatest impact to quality of life is that, without treatment, about 25% of patients will progress to liver failure within 10 years of diagnosis (EASL 2017). Early treatment intervention is critical to prevent or slow progression to end-stage liver disease.

Biomarkers are fundamental to the management of PBC. ALP is recognized clinically as a surrogate marker for risk of disease progression and is the primary predictive and reliable marker of adverse clinical outcomes (Carbone 2013, Lammers 2014). Any reduction in ALP level is considered clinically relevant (EASL 2017, Jones 2024, Murillo Perez 2020, Corpechot 2024). Additional biomarkers used in routine clinical practice for risk assessment and disease monitoring are GGT, AST, ALT, total bilirubin, and transient elastography. Multiple observational studies conducted in large cohorts and registries of patients with PBC have confirmed the correlation between worsening biomarkers and adverse clinical outcomes (Lammers 2014, Corpechot 2022, Murillo Perez 2022, Carbone 2016, Harms 2018, Harms 2019). Elevated biomarkers (AST, ALT) and fibrosis scores (AST to Platelet Ratio Index [APRI], fibrosis-4 [FIB-4]) have been shown to be associated with poor outcomes even in patients who have normalized ALP levels (Victor 2024). Halting progression of liver fibrosis as assessed by transient elastography and serum markers (FIB-4, APRI) has been associated with improved long-term outcomes in PBC (Corpechot 2022).

Pruritus and fatigue are the most common symptoms reported by patients with PBC (Mayo 2008, Crosignani 2008); however, they do not correlate with disease severity or clinical outcomes.

Figure 1: PBC is a Rare, Serious, and Progressive Disease with a Dynamic, Progressive, Pathophysiology



PBC=primary biliary cholangitis

1.2. Treatment Landscape

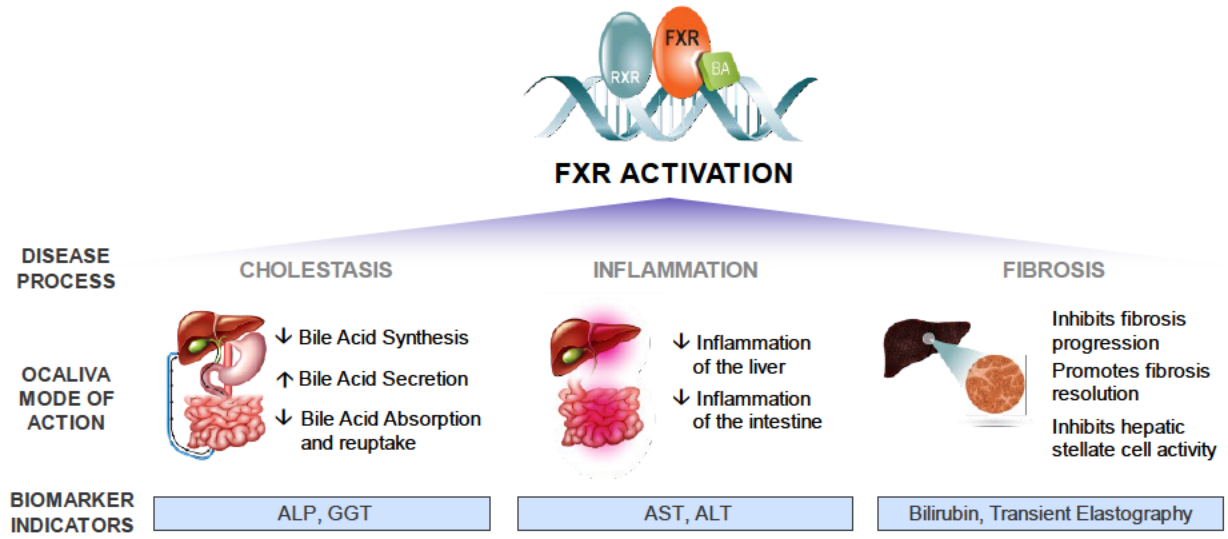
Up to 40% of patients are non-responders to first-line therapy (UDCA), with an additional 5% being intolerant. OCA is the only approved FXR agonist and the only second-line therapy with demonstrated outcomes benefit with over 8 years of clinical use (>42,000 PYs) of postmarketing exposure. Due to the complex autoimmune pathophysiology of PBC, multiple drugs targeting multiple mechanisms of action are needed for treatment.

UDCA is the only approved first-line therapy for PBC (Poupon 1997, Corpechot 2008). As demonstrated by RWE, UDCA therapy has a marked impact on clinical outcomes in PBC (Harms 2019); however, up to 40% of patients have an insufficient response to UDCA (Kowdley 2022, Lindor 2019) based on biochemical thresholds, while 5% are intolerant to UDCA (Invernizzi 2017). In the context of the PBC population in the US, this translates to approximately 45,000 of 100,000 patients who require second-line therapies. These patients remain at significantly increased risk of progressing to liver transplant or death (Kuiper 2009, Lammers 2014).

There is a clear, unmet medical need for second-line therapies for patients with this serious, progressive, life-threatening disease. One in 5 patients with PBC who qualify for second-line therapy but who remain untreated will die, have hepatic decompensation, or be listed for a liver transplant within 5 years (Harms 2019).

Ocaliva is the only approved FXR agonist for second-line therapy in PBC with anti-cholestatic, anti-inflammatory, and anti-fibrotic effects targeting the mechanisms that drive disease progression (Figure 2; Lindor 2019, Gai 2018, Ding 2019, Azizsoltani 2023). UDCA has no meaningful FXR activity and therefore OCA provides a complementary MOA in the treatment of PBC. UDCA's primary mechanism involves increasing the hydrophilicity of the endogenous bile acid pool to render it less cytotoxic. Ocaliva has an additive or synergistic therapeutic benefit when added to UDCA.

Figure 2: Ocaliva Mechanism of Action (Anti-cholestatic, Anti-inflammatory, and Anti-fibrotic)



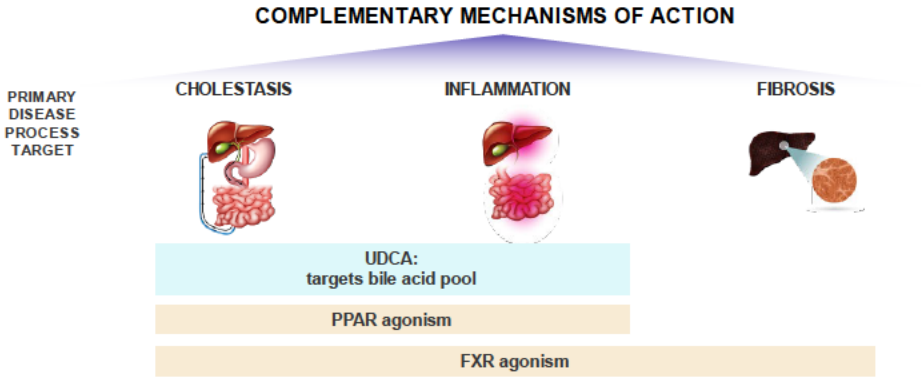
BA=bile acid, FXR=farnesoid X receptor, RXR=retinoid X receptor

Two new PPAR agonists have been recently approved (elafibranor) or are under review (seladelpar) for second-line therapy. OCA's MOA is complementary to both UDCA and the PPAR agonists as these agents do not have anti-fibrotic effects (Figure 3). Evolving data in PBC indicate normalization of ALP and other biomarkers as the new treatment goal, which will likely require use of triple therapy (UDCA + FXR agonist + fibrates [PPAR agonists]) (Gomez 2024).

In addition, Ocaliva is the only approved second-line therapy for PBC with postmarketing experience and evidence of benefit on clinical outcomes. With over 8 years of clinical use (>42,000 PYs), the benefit-risk profile of Ocaliva has been assessed by both Intercept and independent investigators using real-world efficacy and safety data across multiple data sources and studies.

Due to the complex autoimmune pathophysiology of PBC, it is important that multiple therapeutic options with distinct mechanisms of action are available to provide individualized patient care, a paradigm that is well established in the treatment of many chronic diseases, such as hypertension and diabetes. The need for multiple treatment options (including Ocaliva) for PBC management was acknowledged in a recent article published in Hepatology by 25 leading global PBC specialists (Jones 2024).

Figure 3: Multiple Mechanisms of Action are Needed



FXR=farnesoid X receptor; UDCA=ursodeoxycholic acid; PPAR=peroxisome proliferator-activated receptor
Source: Colapietro 2023; Crosignani 2008; Claudel 2011; Verbeke 2016

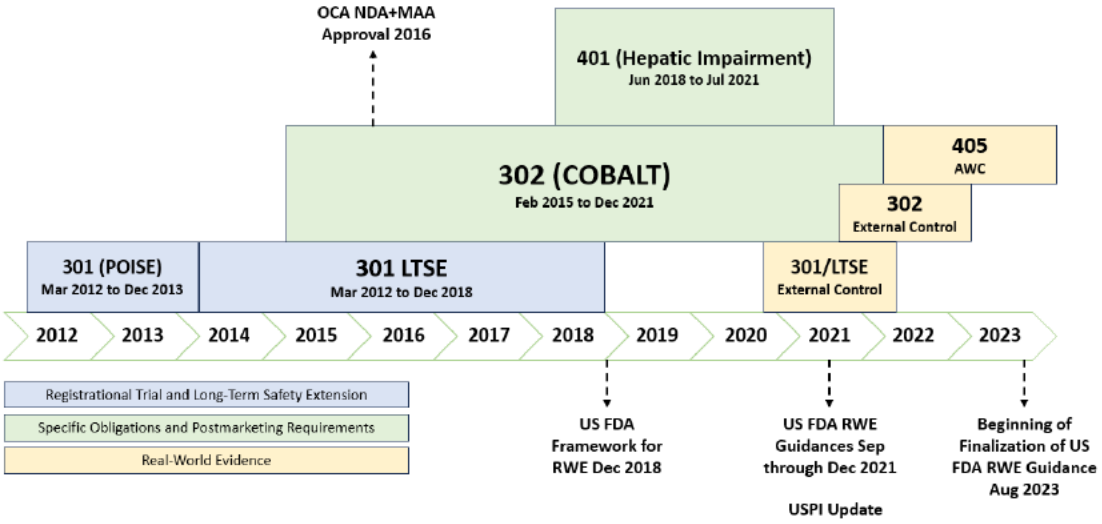
2. DEVELOPMENT OVERVIEW

The Ocaliva clinical development program included studies across the disease spectrum. As clinical experience with Ocaliva accrued, the indication was narrowed over time to focus exclusively on patients earlier in the disease continuum.

Figure 4 presents the chronology of key studies in the OCA clinical development program for PBC:

- The Phase 3 registrational trial (Study 301) that was the basis of accelerated approval
- Clinical studies to fulfill postmarketing requirements (PMRs)
- RWE studies

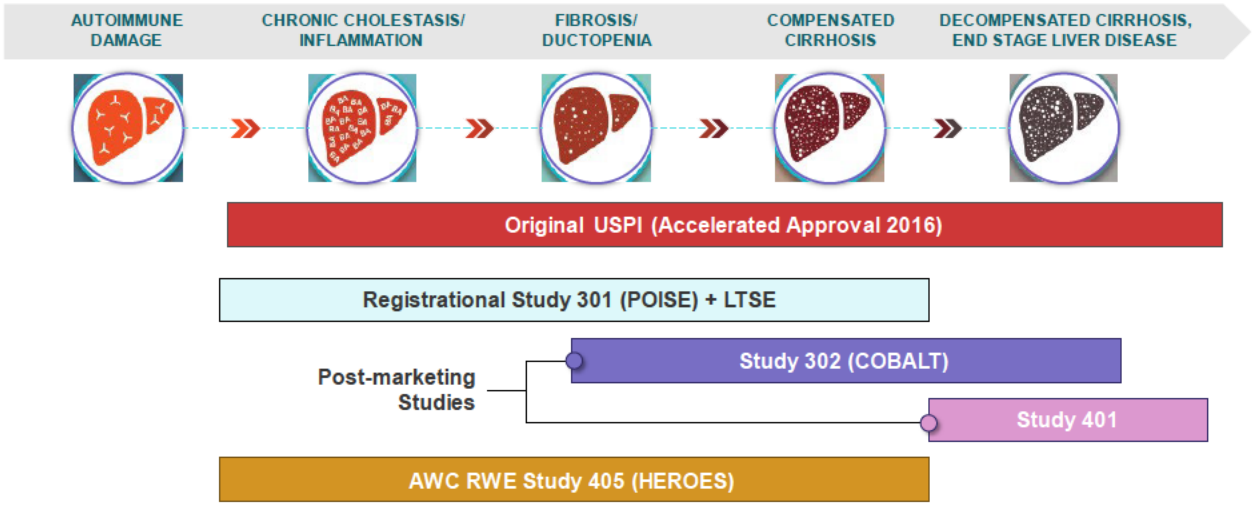
Figure 4: Chronology of Key Studies in OCA Clinical Development Program for PBC



AWC=adequate well-controlled; FDA=Food and Drug Administration; LTSE=long-term safety extension; NDA=New Drug Application; MAA=Marketing Authorization Application; OCA=obeticholic acid; RWD=real-world data; RWE=real-world evidence; US=United States; USPI=United States Prescribing Information

As discussed in the following sections, the Ocaliva clinical development program included studies across the disease spectrum. As clinical experience with Ocaliva accrued, the indication was narrowed over time to focus exclusively on patients earlier in the disease continuum (Figure 5).

Figure 5: PBC Disease Spectrum Studied in Ocaliva Development



AWC=adequate and well-controlled; LTSE=long-term safety extension; PBC=primary biliary cholangitis; RWE=real-world evidence; USPI=United States Prescribing Information

2.1. Registrational Trial and Long-term Safety Extension

Accelerated approval for Ocaliva was granted in the US in May 2016 based on reductions in ALP, a surrogate marker reasonably likely to predict clinical outcomes, in pivotal Phase 3 Study 301. This study recruited patients with PBC who had failed or were intolerant to UDCA, and excluded patients with advanced disease, which reflects the current USPI indicated population. The LTSE of Study 301 was ongoing at the time of accelerated approval and collected up to 5 years of additional data.

2.2. Postmarketing Requirements

Two PMR studies (Studies 302 and 401) were agreed at the time of accelerated approval.

Study 302 was designed to evaluate the effect of Ocaliva on clinical outcomes such as hepatic decompensation, liver transplant, and death. To enrich the study for accrual of hepatic outcome endpoints, the study enrolled patients with more advanced disease.

In 2014, during early design discussions with FDA, Intercept raised concerns about the feasibility of conducting a placebo-controlled trial when Ocaliva would be commercially available and proposed the use of an external control (EC) cohort derived from global PBC patient registries.

As previously anticipated, once Ocaliva was commercially available in 2016, recruitment and retention proved difficult. In 2020, the Data Monitoring Committee (DMC) assessed the feasibility of continued conduct of the study as designed, reviewing a sample size re-evaluation, study discontinuation information, and primary endpoint results along with sensitivity analyses intended to assist the DMC in assessing potential bias in the study. After careful review of all available data, the DMC recommended stopping enrollment in Study 302, stating: "*Study 302 (COBALT) is unlikely to provide evidence of efficacy for the enrolled PBC population as an aggregate or in any subpopulation.*" FDA concurred with the recommendation, and Study 302 was terminated early with 78% of anticipated enrollment. Due to premature study termination, the FDA recommended expanding the primary outcome to include portal hypertension syndromes. Intercept agreed with FDA's recommendation and revised the statistical analysis plan (SAP) prior to unblinding the study.

After accelerated approval, postmarketing pharmacovigilance reports of adverse hepatic events in more advanced patients were observed, which were addressed with a label update in May 2021 to contraindicate patients with a prior decompensation event or compensated cirrhosis who have evidence of portal hypertension. Additional guidance was also provided for monitoring and management of hepatic safety, including instructions for discontinuation if patients become contraindicated over time. Since the 2021 label update, cumulative postmarketing experience shows a significant decrease in risk for serious hepatic events and identified no new safety signals (Section 5.2.1.5). These observations support the selection of the appropriate patient population: patients with early-stage disease who remain at high risk of adverse outcomes having failed UDCA, which is the population reflected in the current USPI (Appendix E, Section 8.5).

Since Study 302 was initiated in 2015 and concluded in 2021—before the current USPI was implemented—a retrospective analysis was conducted in the USPI indicated population (i.e.,

earlier stage disease). The analyses were programmed retrospectively using available baseline data to identify patients indicated per the current USPI. Importantly, these analyses revealed that 55% of patients enrolled in Study 302 would be contraindicated per the current USPI (see Section 4.2.7).

Study 401, a second postmarketing requirement, was designed to assess safety and pharmacokinetics (PK) of OCA in advanced patients with moderate or severe hepatic impairment. Once patients with moderate or severe hepatic impairment became contraindicated during the 2021 labeling update, Intercept terminated Study 401 with 44% (22/50) of anticipated enrollment. Data are summarized in Appendix D, Section 8.4.

2.3. Real-World Evidence

In light of the challenges encountered in completing Studies 302 and 401, Intercept leveraged the availability of commercial OCA for over 8 years (>42,000 PYs of exposure), which provided a robust opportunity to assess the benefit-risk profile of OCA using RWD (e.g., registry and claims databases). These data are important given the inherent challenges of conducting randomized, placebo-controlled, clinical outcome studies once a drug is commercially available, especially for rare diseases with a well-established and easily measurable biomarker in the postmarketing setting (Jones 2024).

RWE is the evidence derived from the analysis of RWD, including data routinely collected from electronic health records, insurance claims, and registries (US FDA 2023d). The importance of considering RWD as part of the totality of evidence package for regulatory decision making was recently acknowledged (Jones 2024).

The RWE package for Ocaliva includes data from multiple data sources, including a US healthcare claims database (Komodo Healthcare Map™), ECs from patient registries (Global PBC, United Kingdom [UK]-PBC), and clinical trials. It employs designs that include observational real-world trial emulation, registry analyses, as well as randomized control trials that are compared to ECs.

Study 405 is an adequate and well-controlled study for this application. This observational, retrospective study compared OCA-treated patients to matched non-OCA-treated patients from the US Komodo Healthcare Map™ database (hereafter referred to as Komodo database). The study was designed in parallel with the release of the FDA draft guidances and adheres to the key principles governing the use of RWD, including reliability and relevance. For the purposes of this guidance, the term reliability includes accuracy, completeness, and traceability. The term relevance includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study.

In addition to Study 405, real-world based studies of varying methodologies across a number of geographies have been conducted including:

- **301 EC**: An EC study that compared OCA-treated patients from the LTSE of Study 301 versus non-OCA-treated patients from the Global PBC and UK-PBC registries (Murillo Perez 2022).

- **302 EC**: An EC study that compared OCA-treated patients from Study 302 versus non-OCA-treated patients from Komodo Health US claims database (Kowdley 2024b).
- **RECAPITULATE**: An Italian independent real-world study, RECAPITULATE, evaluated OCA-treated patients from combined Italian PBC registries versus non-OCA-treated patients from the Global PBC registry (Vespasiani-Gentilucci 2023, Terracciani 2024).

Across the RWE studies, patients were eligible for second-line therapy if they had inadequate response or were intolerant to UDCA. With the exception of Study 302 EC, which included patients with advanced disease, the eligibility criteria in these real-world studies reflect the current USPI indicated population (i.e., patients without decompensated PBC and patients with compensated cirrhosis). The endpoints of transplant-free survival (liver transplant and death) and event-free survival (hepatic decompensation, liver transplant, and death) were evaluated.

Collectively, these data demonstrate a consistent improvement in transplant-free and event-free survival independent of data source, healthcare system, geography, or specific study design.

3. REGULATORY FRAMEWORK FOR APPROVAL

As discussed in Section 2.2, Study 302 was affected by challenges in enrollment and retention of patients once Ocaliva became commercially available and when the USPI contraindicated patients with advanced disease. The study did not meet the primary endpoint. The failure of Study 302 to deliver the expected confirmation of positive clinical outcome emphasizes the difficulty in undertaking placebo-controlled randomized trials for any product in a rare and slowly progressive disease with a well-established and easily measurable biomarker in the postmarketing setting, and in the presence of a commercially available, disease-modifying therapy (Jones 2024).

Senior FDA leaders have stated that there may be many reasons why a confirmatory trial might fail and have emphasized the importance of understanding why a trial did not succeed: *"When trials…do not appear to confirm clinical benefit, FDA must carefully assess each case and consider the underlying reasons and the consequences of all regulatory options, including their potential impact on patients.…Failure to confirm clinical benefit in a completed trial may reflect the possibility that the drug does not in fact confer clinical benefit, but it also may reflect, for example, unforeseen limitations in trial design, rather than clear evidence of lack of effectiveness. The most appropriate regulatory approach must be governed by the unique factors of the particular case,"* FDA in 2009 Government Accountability Office (GAO) Report.

FDA has stated recently that "When a confirmatory trial does not meet its endpoint, it does not necessarily mean that the drug is not effective for the indication approved through accelerated approval."[3]

[3] Letter from Patrizia Cavazzoni, Dkt. No. FDA-2021-P-0268 (Oct. 24, 2022), https://www.regulations.gov/document/FDA-2021-P-0268-0005

Under the FDCA, Sponsors are required to demonstrate "substantial evidence" of effectiveness for approval of a new drug application (NDA) (FDCA Section 505(d) [21 U.S.C. § 355(d)]).[4] FDA has made clear through guidance that it uses a *totality of the evidence* approach when considering the quantity and quality of evidence to support effectiveness for drugs and biological products (US FDA 1998). Many types of data can be used as "confirmatory" evidence to supplement a single adequate and well-controlled trial, and FDA's most recent draft guidance provides as many as seven different examples, one of which is RWD or RWE (US FDA 2023e). FDA also has indicated that such evidence can consist of "supportive data outside of a controlled trial" (US FDA 2019), as well as "studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints." (US FDA 1998). As Commissioner Robert Califf and senior FDA officials also have noted, *"The FDA considers the totality of evidence when evaluating the safety and effectiveness of new drugs. This phrase reflects the nature of drug development, with each successive piece of data building on prior data to provide the quantity and quality of evidence needed to adequately assess risks and benefits."* (Sherman 2017)

RWE has played an increasingly important role in FDA approvals. The 21st Century Cures Act provided that FDA would "establish a program to evaluate the potential use of RWE- (1) to help to support the approval of a new indication for a drug approved under section 355(c) . . . ; and (2) to help to support or satisfy post-approval study requirements." [21 U.S.C. § 355g(1)]. Consistent with this directive, in 2018, FDA published its Framework for FDA's RWE Program and acknowledged that the Agency intended to more fully incorporate RWD and RWE into the regulatory paradigm (US FDA 2018c). As then-Commissioner Scott Gottlieb explained in 2018, "*At the end of a development program, randomized clinical trials can still leave critical questions unanswered, particularly about the effects of a medical product after it is used by a broader population over an extended period. We are using powerful new scientific computing and data storage technologies to enhance our capabilities of gaining valuable information from RWE."* (US FDA 2018d)

FDA's 2018 Framework defined RWE based on analysis of RWD, including data routinely collected from electronic health records, insurance claims, and registries. The Framework also provided guidance for potential use of RWE to support new indications for an approved drug or to satisfy post-approval requirements (US FDA 2018a). *"When properly conducted, a clinical trial with random assignment of participants either to a treatment arm or to a placebo (or other control) arm—optimally promotes the similarity of compared groups regarding such influences, such that a conclusion can be made as to whether differences in outcomes observed between groups can be attributed to the treatment of interest. Nevertheless, for decades FDA has recognized the potential value of other types of controls, including historical controls as a type of EC. Clinical trials using these other types of controls can, when appropriate, serve as the adequate and well-controlled clinical investigations generally required to provide substantial*

[4] "Substantial evidence" is defined in the provision as "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

evidence of effectiveness under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)." (US FDA 2023a)

The FDA has issued a comprehensive set of draft and final guidance documents that guide industry stakeholders interested in providing RWE to support FDA's regulatory decision-making (US FDA 2018b; US FDA 2022; US FDA 2023a; US FDA 2023b; US FDA 2023c; US FDA 2023d; US FDA 2024a; US FDA 2024b).

Collectively, FDA has established that the strength of RWE submitted in support of a regulatory decision depends on the clinical study methodology and the reliability and relevance of the underlying data (US FDA 2018a). Reliability, in turn, includes accuracy, completeness, and traceability (US FDA 2024a). According to FDA, relevance includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study (US FDA 2024a; US FDA 2018a). FDA has recognized that in designing a study relying on RWE, linkages to external data sources, such as disease registries, can be used to enhance the data available on individual patients over time and to provide additional data for validation purposes (US FDA 2024b). FDA has also recognized that under some circumstances, a study relying on RWE can be considered adequate and well-controlled under FDA regulations (US FDA 2021).

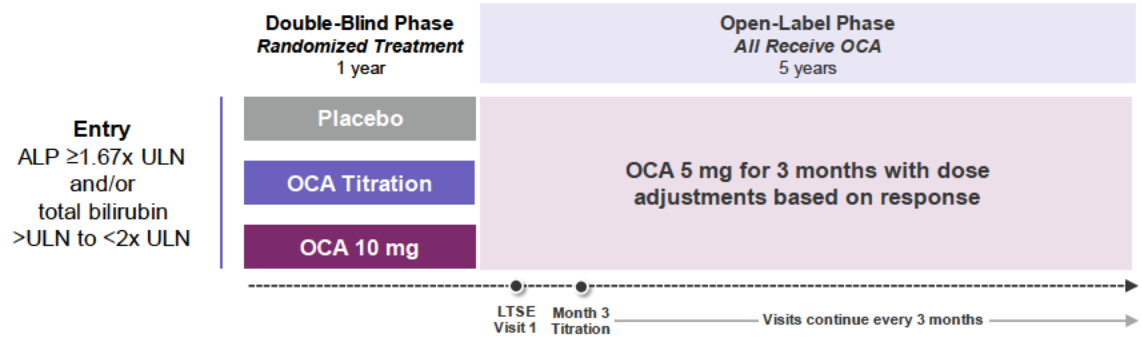
4. EFFICACY RESULTS

The totality of evidence confirms the efficacy of Ocaliva. Study 405, a scientifically adequate and well-controlled observational study, confirms evidence of Ocaliva's benefit on event-free and transplant-free survival. The totality of evidence across the development program demonstrates the favorable impact of OCA on key biomarkers of disease progression including ALP. Results from other real world-based studies across populations and geographies are consistent with the findings of Study 405.

4.1. Study 301/301 LTSE

Study 301 formed the basis of accelerated approval based on improvement in ALP, a surrogate marker reasonably likely to predict clinical outcomes. The LTSE of Study 301 was ongoing at the time of accelerated approval and collected up to 5 years of additional data (Figure 6).

Figure 6: Study 301/301 LTSE – Design



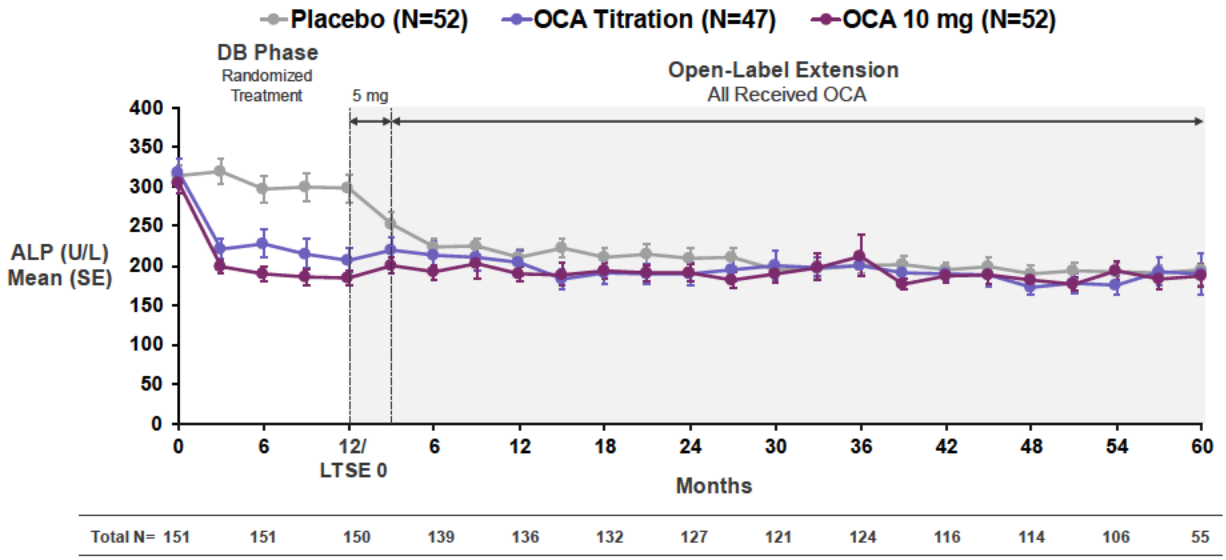
LTSE=long-term safety extension; OCA=obeticholic acid

The primary efficacy endpoint of the DB phase was percentage of patients with ALP <1.67x ULN and total bilirubin ≤ULN and an ALP decrease of ≥15% from baseline at Month 12. The primary analysis compared the response rates in the OCA 10 mg group and the placebo group. A total of 34 (47%) subjects from the OCA 10 mg group achieved the primary endpoint, compared with 7 (10%) subjects from the placebo (p <0.0001). The difference between placebo and the OCA titration group was also statistically significant (p <0.0001). The response to OCA therapy was rapid and robust with clinically meaningful reductions in ALP apparent within 2 weeks of treatment and at every timepoint thereafter, compared to placebo where ALP levels remained highly elevated.

Results were sustained throughout the LTSE period for OCA-treated patients for both the primary endpoint (Appendix B, Section 8.2.1) and ALP (Figure 7), up to 60 months.

In addition, patients who had been randomized to placebo during the DB phase and transitioned to OCA during the LTSE exhibited a nearly identical response to OCA as patients who had been originally randomized to the OCA treatment groups (Figure 7). Clinically significant and sustained reductions were also observed in other serum markers of cholestasis (GGT) and hepatocellular injury (ALT, AST) throughout the LTSE period (Appendix B, Section 8.2.1).

Figure 7: Study 301 LTSE – ALP



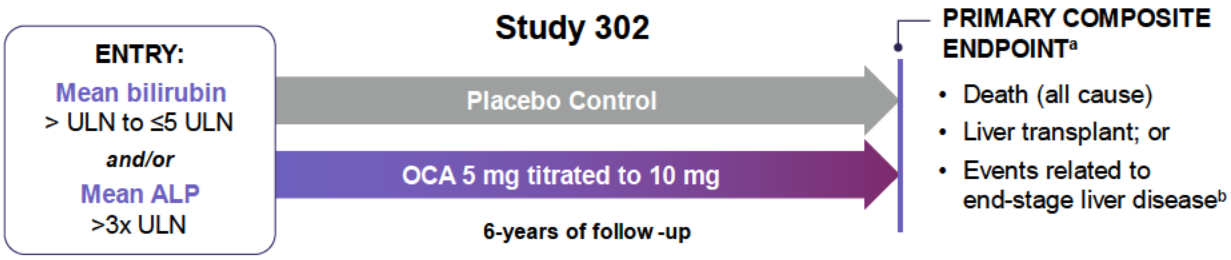
DB=double blind; LTSE=long-term safety extension; OCA=obeticholic acid; WADD=weighted average daily dose
Note: To account for flexibility of dose adjustments and titration, data are presented by WADD. Of the 193 patients who enrolled into the LTSE phase, 151 (78%) received a WADD of ≤10 mg (consistent with the approved marketed doses of 5 mg or 10 mg).

4.2. Study 302

4.2.1. Study Design

Study 302 was the largest, randomized, placebo-controlled study conducted in patients with PBC eligible for second-line therapy. The study was enriched with a more advanced PBC population than Study 301 in order to capture the long-term outcomes of interest. The inclusion criteria required a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN. A total of 69 (21%) patients with evidence of decompensated cirrhosis were enrolled.

Figure 8: Study 302 – Design



[a] Original primary endpoint.
[b] Events related to end-stage liver disease included MELD score ≥15, uncontrolled ascites, or hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.
OCA=obeticholic acid

Per ITT principle, the design specified that patients who discontinued investigational product and remained in Study 302 continue to contribute to the primary efficacy analysis as randomized. In some cases, this included patients who began other active therapies such as commercial Ocaliva or unapproved second-line treatments for PBC (e.g., bezafibrate or fenofibrate).

4.2.2. Study Population

At the time of study termination, a total of 334 patients of the planned 428 were randomized in the study and were included in the ITT Population (168 patients in the OCA group and 166 patients in the placebo group).

Based on enriched eligibility criteria, patients in confirmatory Study 302 had more advanced disease compared to the patients in Study 301. Patients in Study 302 had ~40% higher baseline ALP and more than double baseline total bilirubin (Table 1).

Table 1: Baseline Disease Severity Comparison: Study 301 and 302 (ITT Population)

	Study 301 (DB Phase)		Study 302	
	Placebo (N=73)	OCA Titration[a] (N=70)	Placebo (N=166)	OCA (N=168)
ALP (U/L), Mean (SD)	327.5 (115.0)	325.9 (116.2)	499.3 (294.5)	481.3 (276.7)
ALP >3x ULN, n (%)	23 (32)	19 (27)	104 (63)	103 (61)
Total Bilirubin (mg/dL), Mean (SD)	0.69 (0.43)	0.60 (0.32)	1.65 (0.80)	1.57 (0.76)
Total Bilirubin >ULN, n (%)	7 (10)	4 (6)	117 (71)	118 (70)

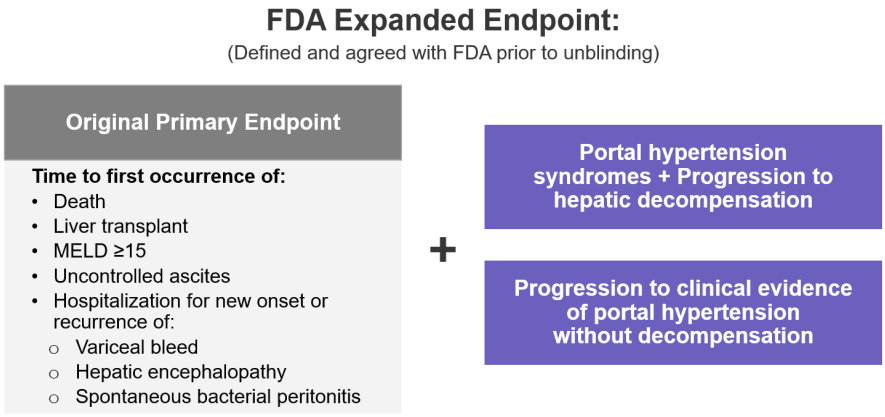
ITT=Intent-to-Treat; OCA=obeticholic acid

[a] Patients randomized to the OCA titration treatment group received 5 mg OCA as their starting dose. Only OCA titration patients eligible for titration at Month 6 up-titrated to 10 mg OCA while patients ineligible for titration remained at their starting dose of 5 mg OCA.

4.2.3. Primary Endpoint Modifications

In order to increase power and allow better precision in estimation of the treatment benefit, the original primary endpoint was expanded prior to database lock based on recommendations from the FDA. This included the addition of clinically relevant events such as portal hypertension syndromes, progression to hepatic decompensation (for patients without decompensation at baseline), and progression to clinical evidence of portal hypertension without decompensation (for patients without decompensation or clinical evidence of portal hypertension at baseline) (Figure 9).

Figure 9: Study 302 – Expanded Primary Endpoint



FDA=Food and Drug Administration; MELD=Model End-Stage Liver Disease
Note: The detailed definition of the of the expanded primary endpoint by group is presented in Appendix B, Section 8.2.2.2.

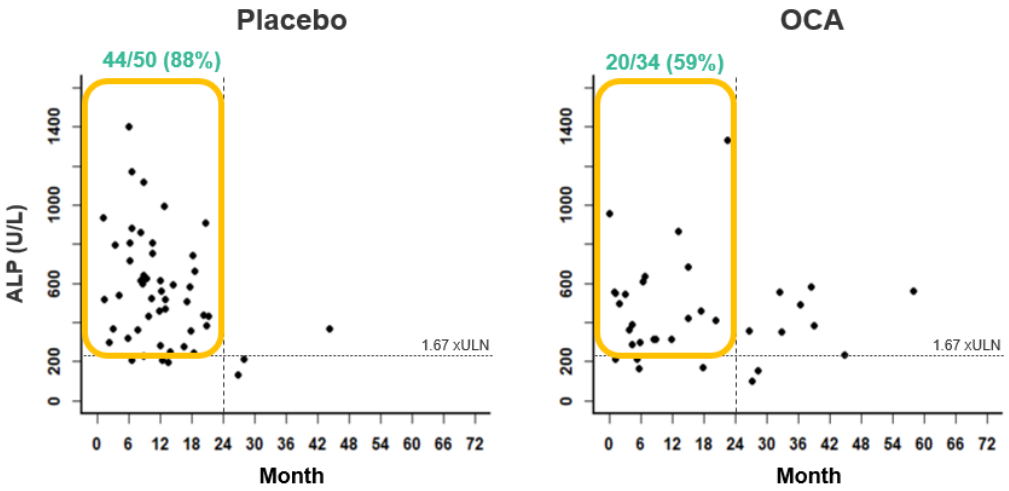
4.2.4. Bias

The pre-specified ITT analysis was designed to compare patients treated with OCA to patients not treated with OCA. However, inherent challenges in conducting a placebo-controlled trial in the setting of commercially available therapies (e.g., commercial Ocaliva or other active therapies such as fibrates and/or UDCA if not on UDCA at baseline) introduced 2 forms of bias.

Functional Unblinding: Easy access to serial ALP testing to monitor PBC progression and response to treatment led to early discontinuation in patients with elevated ALP, especially evident in placebo patients.

A total of 50/166 (30%) of placebo patients and 34/168 (20%) of OCA patients discontinued study visits or initiated commercial therapy prior to an endpoint event. The time course for these observations is relevant to the final outcome of the study: A higher number and proportion of patients in the placebo group (44/50 [88%] compared to the OCA group (20/34 [59%]) discontinued study visits or initiated commercial therapy within the first 24 months and had a high ALP (≥1.67x ULN) (Figure 10).

Figure 10: Study 302 – Mean ALP at Time of Study Visit Discontinuation and/or Initiation of Commercial Therapy Prior to an Endpoint Event



OCA=obeticholic acid

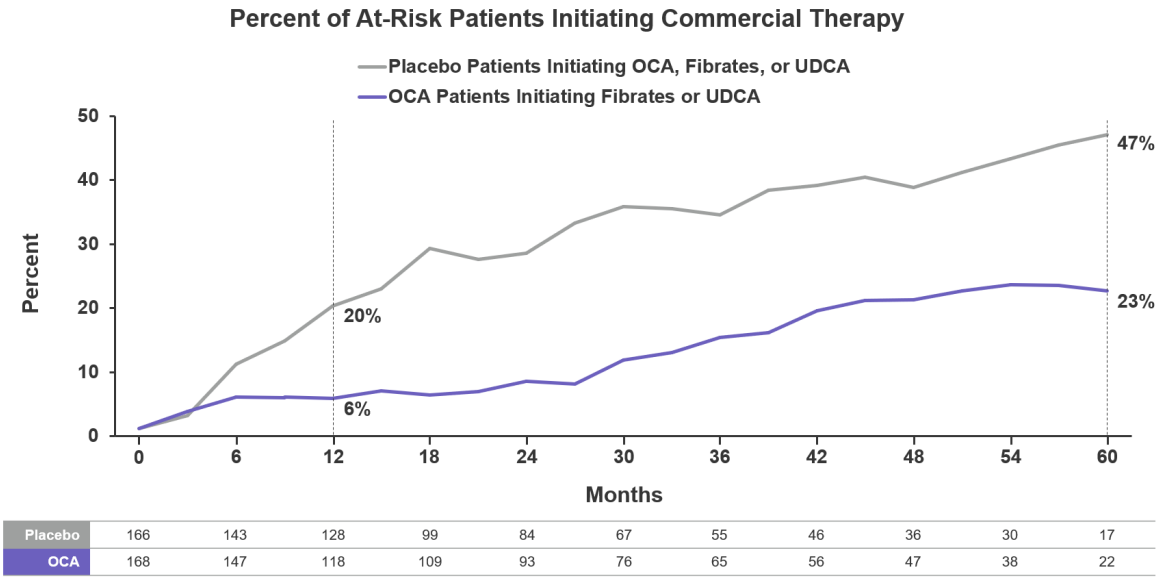
Treatment Crossover: Treatment crossover from randomized treatment to commercial Ocaliva or another active therapy was observed in more patients in the placebo group compared to patients in the OCA group who remained in the study. Per ITT principles, these patients were still evaluated per their randomized treatment.

In an ideal treatment-placebo comparison, no patients would be on a commercial therapy. In Study 302, patients could initiate commercial Ocaliva or another active therapy but remained in the ITT analysis as randomized. In these patients, switching to commercial therapy would be expected to impact the disease pathway and time course of clinical outcomes.

To evaluate the impact of switching to commercial therapy, an analysis was performed to evaluate the percentage of patients who were on a commercial Ocaliva or another active therapy out of those patients who were still contributing to the survival curve (i.e., at risk) over time.

As shown in Figure 11, at 12 months of study enrollment, 20% of patients in the placebo group at risk for an endpoint event had initiated active therapy compared to 6% of at-risk patients in the OCA group. After 5 years of the study, 47% of patients remaining at risk in the placebo group initiated active therapy compared to 23% of at-risk patients in the OCA group.

Figure 11: Study 302 – Patients Initiating Commercial Therapy Overtime



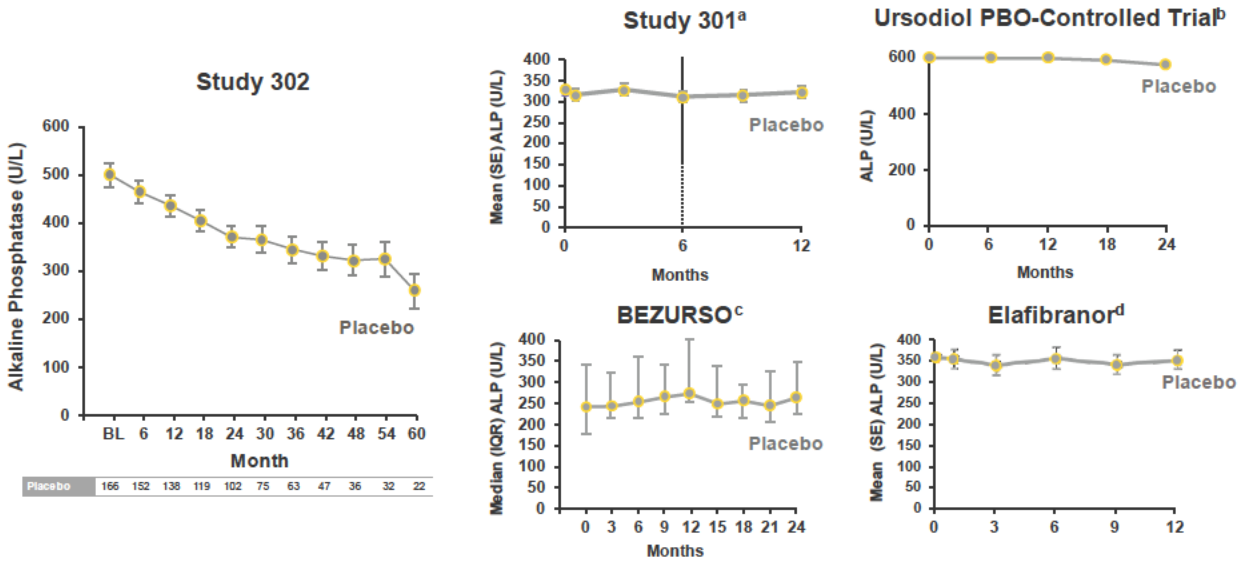
Placebo	166	143	128	99	84	67	55	46	36	30	17
OCA	168	147	118	109	93	76	65	56	47	38	22

OCA=obeticholic acid; UDCA= ursodeoxycholic acid
Commercial therapy for placebo = commercial OCA and/or fibrates and/or UDCA if not on UDCA at baseline
Commercial therapy for OCA = fibrates and/or UDCA if not on UDCA at baseline. Commercial Ocaliva not included as it is equivalent to maintaining investigational product (i.e., OCA).

Impact of Functional Unblinding and Treatment Crossover

The impact of functional unblinding and crossover in the placebo arm of Study 302 is shown in Figure 12. On the left, there is a clear downward trend in longitudinal ALP among placebo patients remaining in Study 302 through 5 years, which is not expected based on known PBC disease pathophysiology. On the right, numerous clinical studies in patients with PBC have consistently shown stable ALP levels in placebo-treated patients. The unexpected trend in the placebo arm in Study 302 demonstrates the likely impact of treatment crossover introducing bias into the ITT primary outcomes effect estimate over the course of follow-up.

Figure 12: Mean/Median ALP in Placebo-Randomized Patients in PBC Studies



CSR=clinical study report; PBC=primary biliary cholangitis; PBO=placebo
[a] Study 301 CSR
[b] Adapted from Combes 1995 (publication does not specify whether data are mean or median)
[c] Adapted from Corpechot 2018
[d] Adapted from Kowdley 2024a

4.2.5. Primary Endpoint

As shown in Table 2, while the estimated hazard ratio (HR) (95% CI) for the expanded primary endpoint, as agreed with FDA, showed a shift towards benefit with an estimated HR of 0.84 (0.61, 1.16); the HR for the original primary endpoint was 1.01 (0.68, 1.51).

Table 2: Study 302 – Time to the First Occurrence of Primary Clinical Outcome Event (ITT Population)

Statistics	Primary Composite Endpoint			
	Original Primary Endpoint		Primary Expanded Endpoint	
	Placebo (N=166)	OCA (N=168)	Placebo (N=166)	OCA (N=168)
Number of Patients with Clinical Event, n (%)	48 (28.9)	48 (28.6)	80 (48.2)	71 (42.3)
Log Rank p-value[a]	0.954		0.304	
HR (95% CI)[b]	1.01 (0.68, 1.51)		0.84 (0.61, 1.16)	
IPCW HR (95% CI)[c]	0.82 (0.53, 1.27)		0.80 (0.58, 1.12)	

HR=hazard ratio; ITT=Intent to treat; IPCW=inverse probability of censoring weighting; IWRS=interactive web response system; OCA=obeticholic acid
Note: Percentages are based on number of patients in the ITT Population within each treatment group.
[a] Log-Rank p-value was based on log-rank test stratified by the randomization stratification factor.
[b] HR was estimated using stratified Cox's proportional hazards model with treatment group as an independent variable and the randomization stratification factors as entered in the IWRS as strata. The results represent the ratio of OCA to placebo. A HR <1 indicates an advantage for OCA.
[c] IPCW estimator corrects for informative censoring. This estimator corrects for informative censoring of patients by giving extra weight to similar patients who are not censored.

4.2.6. Sensitivity Analyses

As designed, per ITT principles, patients who discontinued treatment but remained in Study 302 continued to contribute to the primary efficacy analysis in their randomly assigned treatment arm (placebo N=166; OCA N=168) even in cases when patients initiated commercial Ocaliva or unapproved second-line treatments for PBC, e.g., bezafibrate or fenofibrate.

Because functional unblinding and treatment crossover compromised the ITT analysis, sensitivity analyses were performed on the FDA expanded endpoint to assess whether differential discontinuation and treatment crossover impacted the observed treatment effect.

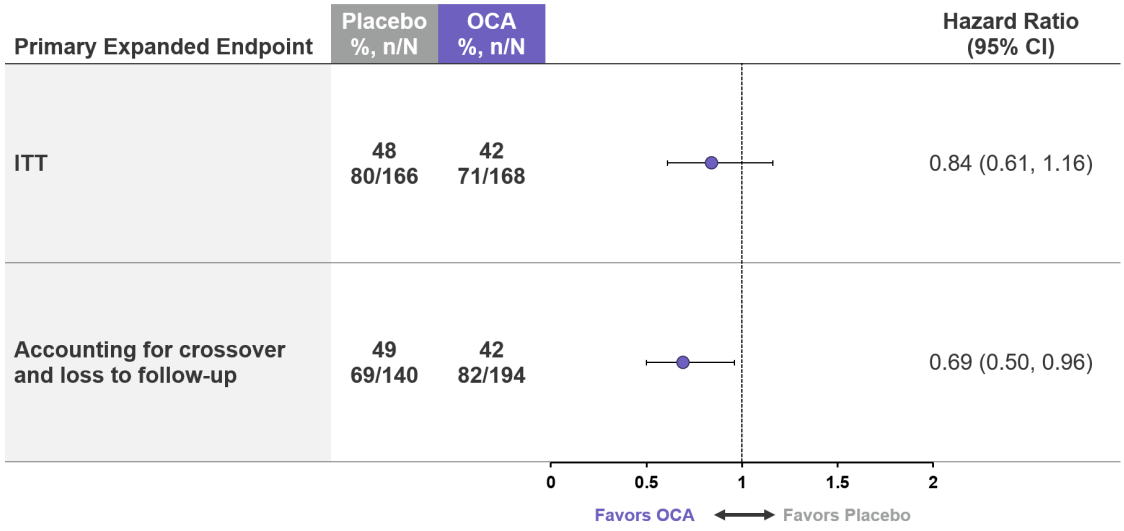
The impact of these confounding variables was assessed by prespecified inverse probability of censoring weighting (IPCW) analyses. The IPCW estimator is a method to adjust for informative censoring (Robins 1993).

Informative censoring occurs when there is a relationship between the probability of being lost to follow-up and the probability of an event. For example, if sicker patients with higher ALP and advanced disease are more likely to drop out from a study (i.e., patients with shorter time-to-death), these patients are lost to follow-up prior to experiencing the event of interest. A statistical model that does not account for informative censoring will therefore overestimate survival time. The IPCW estimator corrects for informative censoring of patients by giving extra weight to similar patients who are not censored. If the IPCW estimator differs from the unweighted estimator, one can conclude informative censoring is impacting the analysis.

Applying the IPCW estimator to Study 302 adjusts for informative censoring due to study discontinuation but does not adjust for the use of commercial therapies such as fibrates, which occurred at different rates between the two treatment groups and is expected to bias the estimator towards the null. Therefore, a post-hoc analysis was also performed by classifying placebo crossover patients as "OCA-exposed." A total of 26 patients in the placebo group who received commercial OCA were re-classified as OCA-treated (placebo N=140; OCA N=194).

The results are presented in Figure 13. When correcting for treatment crossover and informative censoring, the effect of treatment shifts in favor of OCA and 95% CI excludes unity (value of no treatment effect). A HR of 0.69 provides clinically meaningful evidence of benefit in reducing the risk of serious adverse hepatic outcomes including liver transplant and death, especially when considering that it likely underestimates the treatment effect since this analysis does not correct for all sources of bias.

Figure 13: Study 302 – Primary Expanded Endpoint and Sensitivity Analysis

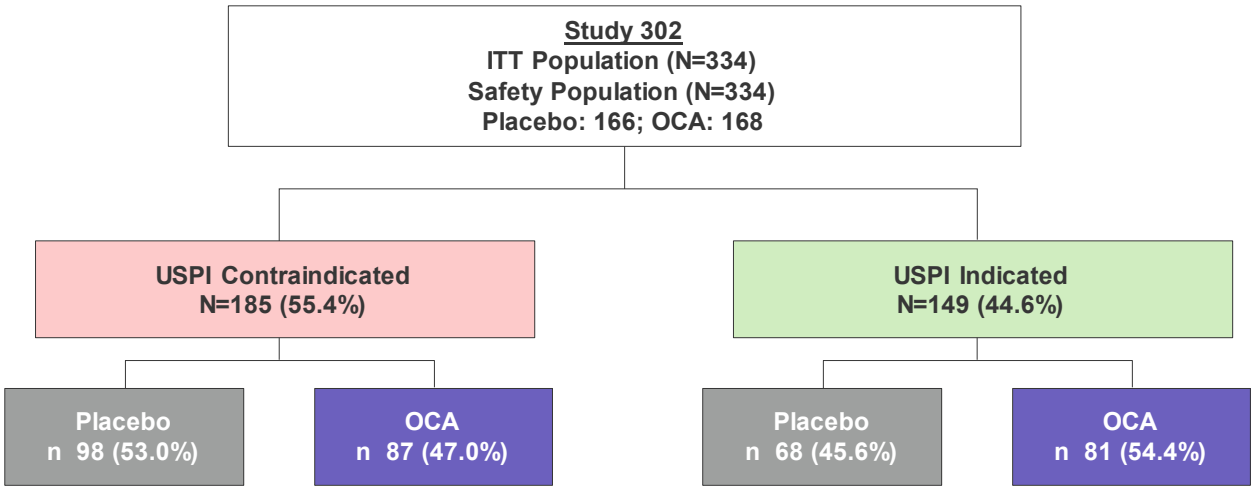


ITT=intent to treat; OCA=obeticholic acid
Note: Loss to follow up based on IPCW adjusting for informative censoring.

4.2.7. Subgroup Analyses

Since Study 302 was initiated in 2015 and concluded in 2021—before the current USPI was implemented— retrospective analyses were conducted in the USPI subgroup (indicated versus contraindicated population). The analyses were programmed retrospectively using available baseline data. Importantly, these analyses revealed that 55% of patients enrolled in Study 302 would be contraindicated per the current USPI (Figure 14).

Figure 14: Study 747-302 – Subgroups by USPI Indication Status at Baseline



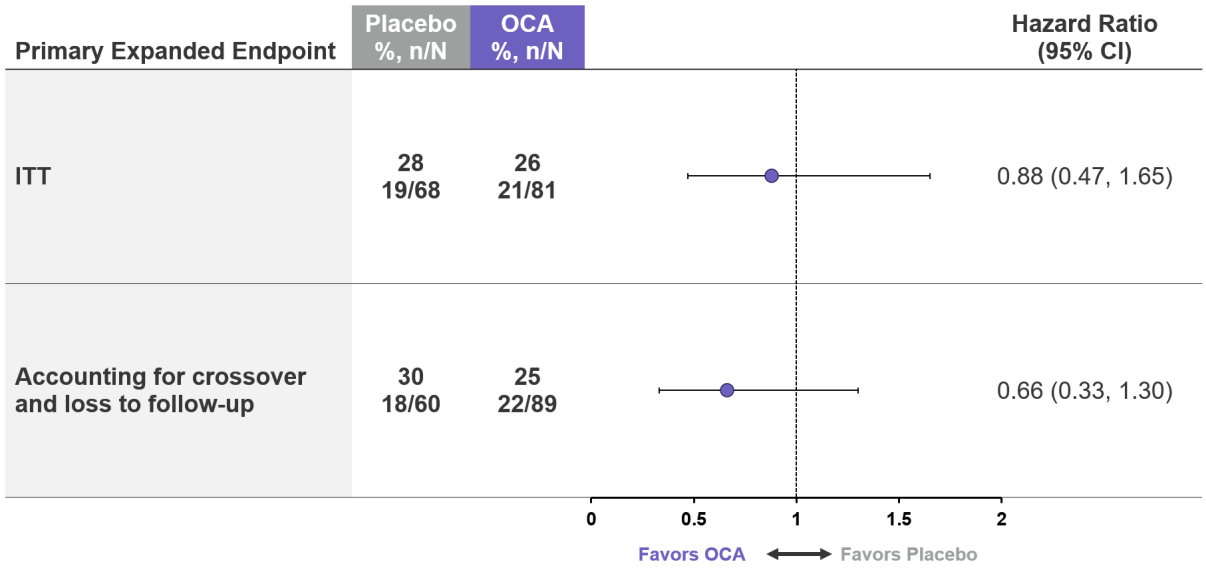
ITT=intent-to-treat; OCA=obeticholic acid; PH=portal hypertension; USPI=United States Prescribing Information
Note: The USPI indicated population included patients who had not experienced PH or decompensation at baseline. The USPI contraindicated population included patients who had experienced PH and/or decompensation at baseline.

The Sponsor acknowledges inherent limitations of these analyses including:

- All data necessary to define the USPI subgroup criteria at baseline was not collected prospectively during enrollment as the change of indicated population in USPI updates occurred after the last patient had been enrolled in the study. Thus, the subgroup analysis populations were grouped and programmed retrospectively using available baseline data.
- While there is a high degree of certainty that patients are appropriately excluded from the USPI subgroup (i.e., patients categorized as contraindicated are expected to be truly contraindicated); there are a few patients who were programmatically classified as indicated per the USPI at baseline but who have data external to the case report forms (CRFs) (e.g., from medical records available as part of a serious adverse event (SAE) or clinical endpoint source records) suggest they were contraindicated at baseline.
- The percentage of patients in each treatment arm is not balanced within the USPI subgroup and randomization strata (UDCA treatment [yes/no] and mean baseline bilirubin categories [>ULN/≤ULN]) are not balanced within treatment arm within the USPI subgroup as this is a retrospectively defined subgroup.
- Patients who became contraindicated on-study continued to receive study drug which is contrary to the current label guidance.

Acknowledging these inherent limitations of this subgroup analysis, similar to the full Study 302 population, a shift in the estimated HR for clinical outcomes is seen in OCA-treated patients compared to placebo-treated patients in the USPI indicated population when adjusting for treatment crossover and informative censoring (Figure 15).

Figure 15: Study 302 – Primary Expanded Endpoint and Sensitivity Analysis in USPI Indicated Subgroup



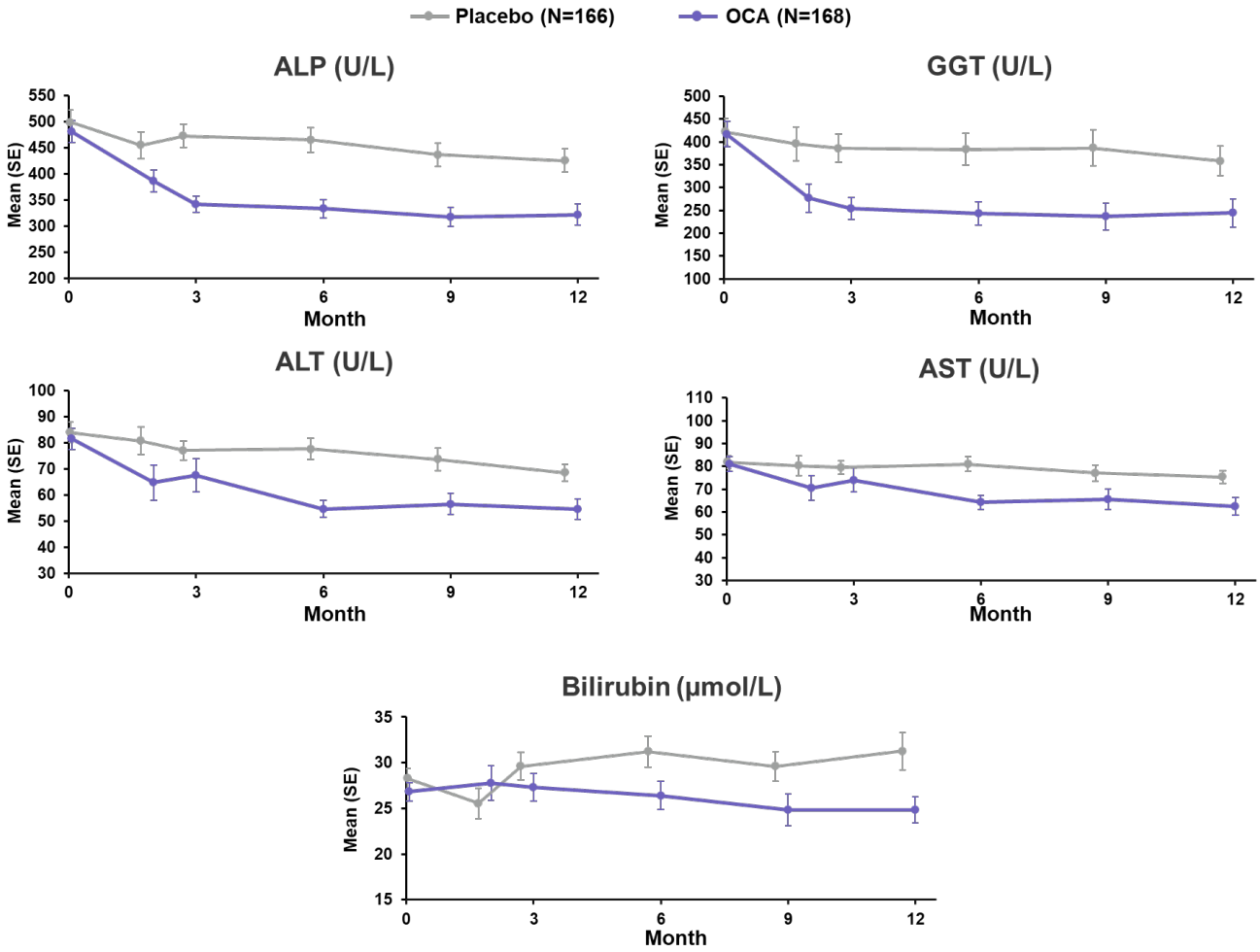
ITT=intent to treat; OCA=obeticholic acid
Note: Loss to follow up based on IPCW adjusting for informative censoring.

4.2.8. Biochemical Markers

Biochemical response was evaluated over the initial 12 months of the DB period of Study 302 during which time impact of lost to follow-up and treatment crossover was limited.

Despite a higher baseline for ALP in Study 302, there was a rapid and sustained decline in ALP for OCA-treated patients that was similar to what was observed in Study 301. This pattern was consistently observed in all other continuous liver biochemistry measures (See Figure 16).

Figure 16: Study 302 – ALP, GGT, ALT, AST, and Bilirubin (Safety Population)



Note: To minimize the effect of the treatment crossover, the analyses included data from initiation of investigational product to 30 days after discontinuation of investigational product (i.e., the Safety Population) and excluded data after commercial OCA initiation.

4.3. Real-World Evidence Studies

To further explore the effectiveness of Ocaliva, Intercept conducted an adequate and well-controlled Study 405, which demonstrated a statistically and clinically meaningful treatment benefit for event-free and transplant-free survival.

4.3.1. Study 405

4.3.1.1. Study Design

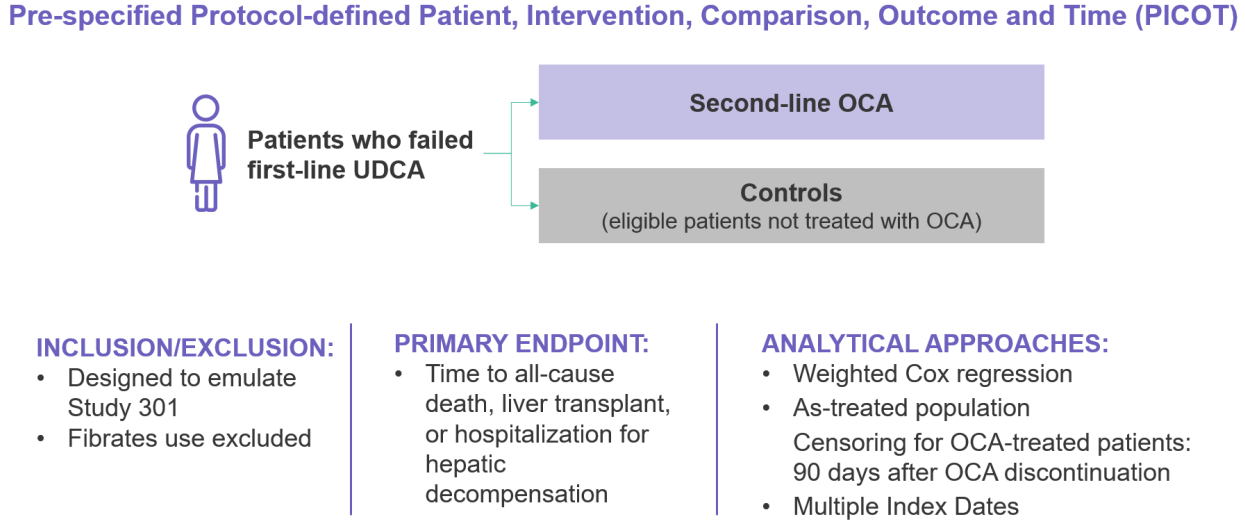
Study 405 is an adequate and well-controlled observational, retrospective trial emulation of Study 301 using the US Komodo Healthcare Map™ administrative claims database. Patient, Intervention, Comparison, Outcome and Time (PICOT) for Study 405 were pre-specified and adhered to FDA RWE guidances.

The study analyzed patients who had failed first line treatment UDCA, and compared patients using OCA as a second line therapy to patients who were eligible for OCA, but not using OCA. The patient population generally reflects the current USPI indicated population and aligns with Study 301, which excluded patients with more advanced disease.

The primary endpoint was the first event of the composite endpoint of all-cause death, liver transplant, or hospitalization for hepatic decompensation.

The pre-specified analysis plan employed an as-treated approach (i.e., censoring for OCA-treated patients 90 days after OCA discontinuation), which is the standard convention for observational studies that evaluate the association between exposure/treatment and outcomes for patients on chronic therapy in the real-world clinical practice setting. The trial emulation design utilized multiple index dates (see Appendix B, Figure 33).

Figure 17: Study 405 – Observational, Retrospective Trial Emulation Using the Komodo Claims Database



OCA=obeticholic acid; UDCA=ursodeoxycholic acid; US=United States
Protocol 405 (ClinicalTrials.gov/NCT05292872)
All patients who met diagnostic and eligibility criteria between 01 Jun 2015 and 31 Dec 2021 from the Komodo database were considered for this study (see Section 4.3.1.3).

4.3.1.2. Data Source Assessment and Selection

A comprehensive, rigorous process was used to evaluate multiple data sources in order to select one that was fit-for-use to answer the primary objective of the protocol. Five large databases were evaluated for fit-for-use: Komodo Healthcare Map™ claims database, Optum claims database, Global PBC and UK-PBC registries, and Target RWE electronic health care records. Per FDA guidance this included an assessment of the reliability and relevance of the database (Table 3).

Table 3: Study 405 – Fit for Use Evaluation: Reliability and Relevance Assessment

Fit-for-Use Criteria	Description	Komodo Claims	Optum Claims	Global-PBC and UK PBC Registry	Target-RWE EHR-based
RELIABILITY					
Data Accrual	Hard outcomes well captured independent of OCA use	✓	✓	✓	✓
Data Quality and Integrity	Quality control; completeness, accuracy and consistency	✓	✓	✓	✓
RELEVANCE					
Data Availability	Database capturing patients with PBC with long-term follow-up	✓	✓	✓	✓
	Sufficient detail to evaluate the question (e.g., hospitalization for hepatic decompensation)	✓	✓		✓
Generalizability	Large database of OCA-treated patients for a well-powered analysis, representative of population eligible for use	✓		✓	
Timeliness	Contemporaneous data capture for both treated and control groups	✓	✓		
Linkages	Predefined, scientifically valid methodology using Datavant technological leader	✓	✓		✓

The availability of relevant confounder data was generally similar across RWD databases.
OCA=obeticholic acid; PBC=primary biliary cholangitis; RWD=real-word data; RWE=real-world evidence; UK=United Kingdom

All databases captured the hard outcomes of hepatic decompensation, liver transplant, and death in a consistent and methodical manner; and each employed rigorous quality assurance procedures. The Komodo Healthcare Map™ database was ultimately selected based on key relevance features as described below.

Data Availability

The Komodo database is a nationally representative longitudinal database that includes de-identified claims-based healthcare encounters from 325 million insured individuals across more than 150 commercial, Medicare, and Medicaid payers from all 50 US states. As a closed claims database, all claims have undergone a thorough review by insurers prior to payment.

Komodo captures a large number of OCA-treated and OCA-eligible but non-OCA-treated (control) patients with PBC with up to 5 years of follow-up to observe the outcomes of interest. The Komodo claims database had a similar prevalence (~40 patients per 100,000) and demographics (>80% female, age ~60 years, just under 50% non-white race/ethnicity) to another large analysis of a claims database (Fibrotic Liver Disease [FOLD] Consortium) in the peer reviewed literature (Lu 2018a, Lu 2018b; Appendix B, Section 8.2.3.1).

Generalizability

The Komodo database was representative of OCA-treated patients in the US ensuring generalizability of findings for OCA use in the real-world, enabling a well-powered analysis of eligible patients. Specifically, the database included one-third of all patients using OCA in US (Komodo, N=2,552; Intercept Database [internal data of patients using Ocaliva during timeframe], N=7860). It also utilized Study 301 inclusion and exclusion criteria and was generally consistent with the USPI and OCA use in clinical practice. As shown in Table 4, baseline characteristics in the real-world OCA-treated group in Study 405 generally aligned with those of the OCA-treated group in Study 301.

Table 4: Baseline Characteristics – OCA-treated Patients in Study 405 vs Study 301

	Study 405 OCA-Treated N=403	**Study 301 OCA Titration[a] N=70**
Age, Mean (SD)	56.2 (10.6)	55.8 (10.5)
Female, n (%)	369 (92)	65 (93)
ALP (U/L), Mean (SD)	292.1 (154.2)	325.9 (116.2)
Total Bilirubin (mg/dL), Mean (SD)	0.70 (0.46)	0.60 (0.32)

OCA=obeticholic acid

[a] Patients randomized to the OCA Titration treatment group received 5 mg OCA as their starting dose. Only OCA titration patients eligible for titration at Month 6 up-titrated to 10 mg OCA while patients ineligible for titration remained at their starting dose of 5 mg OCA.

Timeliness

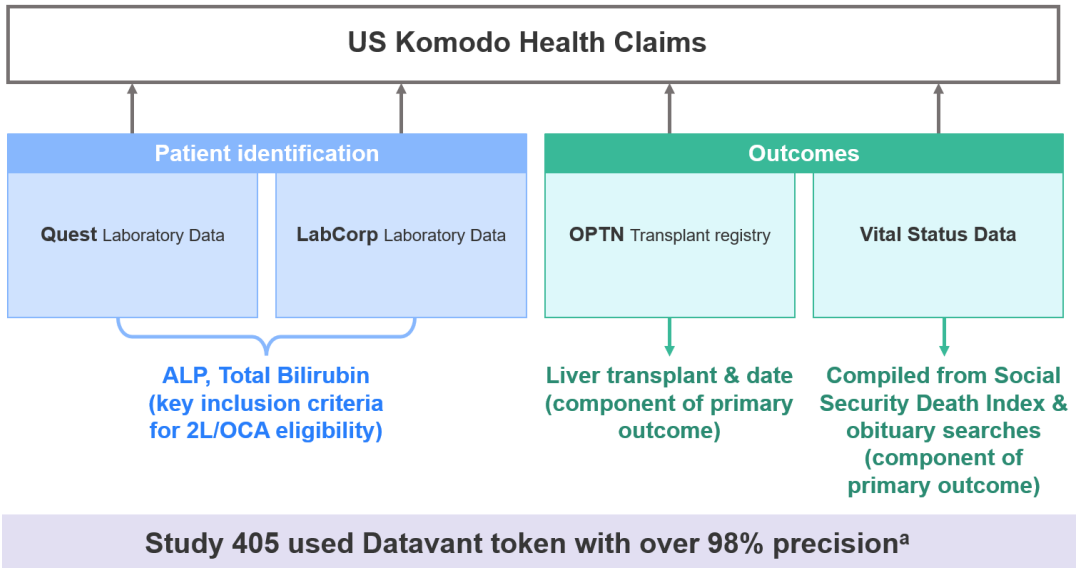
The Komodo database included contemporaneous data collection of all necessary variables for cohort identification and outcomes capture for both OCA-treated and non-OCA-treated cohorts. The data were collected in the post Ocaliva approval time period starting in 2016 with database closure in 2021 and analyses performed in 2022.

Linkages

The Komodo database had the ability to link to four supplemental data sources to strengthen the rigor and ensure capture of relevant data points (Figure 18). To enhance patient identification and assess key inclusion criterion, claims were linked with laboratory data from LabCorp® and Quest Diagnostics®, which together account for more than half of outpatient labs in the US. Further, to enhance outcomes collection, data were linked with data from the Organ Procurement and Transplantation Network (OPTN), a registry that captures US transplant information (including donors, waitlisted candidates, and transplant recipients), as well as the vital status derived from Social Security Death Index and Obituary Search (SSDI + obituary search) database to ascertain date of death.

The US databases have established privacy-preserving linkage procedures that allow them to implement tokenization and linkage with other RWD bases (Figure 18). All data were linked to Komodo using Datavant tokenization methodology, a leader for linking RWD while protecting personally identifiable information (PII), with over 98% precision (Bernstam 2022).

Figure 18: Study 405 – Supplemental Data Strengthen Patient Identification and Outcomes Collection



2L=second-line therapy; OCA=obeticholic acid; OPTN=Organ Procurement and Transplantation Network; US=United States
[a]Bernstam 2022

4.3.1.3. Patient Eligibility and Exclusion Criteria

Definition and Validation of PBC Diagnosis

Per the American Association for the Study of Liver Diseases (AASLD) guidelines, PBC diagnosis is based on the presence of ≥2 of 3 diagnostic factors:

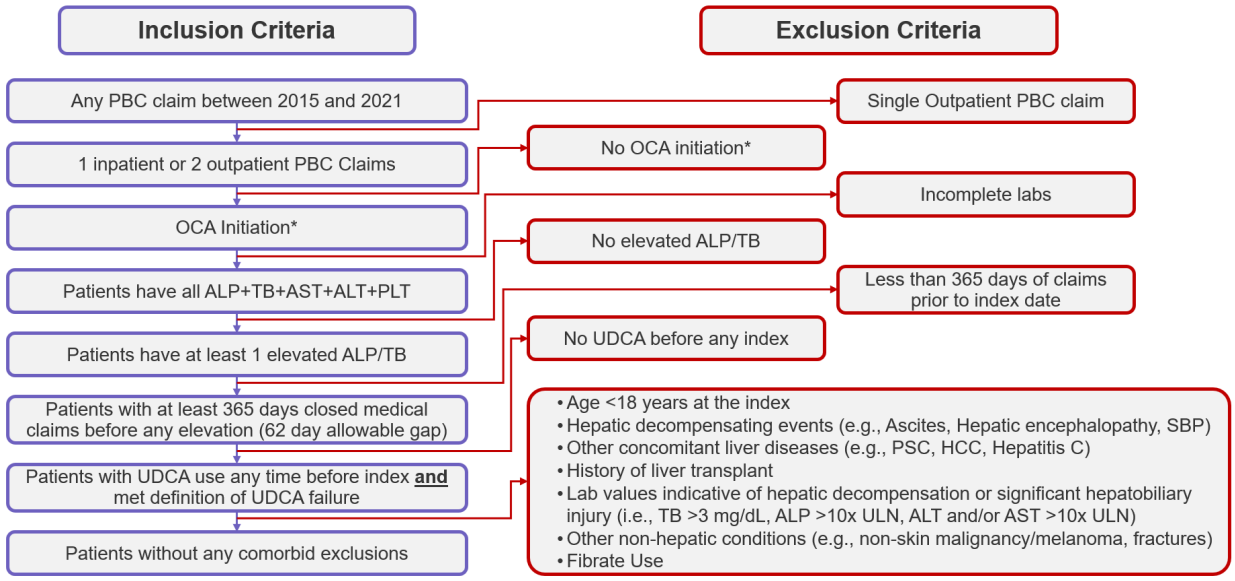
- History of elevated ALP levels for at least 6 months
- Positive anti-mitochondrial antibodies (AMA) titer
- Liver biopsy finding consistent with PBC

AMA is normally assessed once to diagnose PBC, and the test may have occurred years prior to entry into the Komodo Health claims database. A preliminary analysis showed that ~10% of patients with a PBC diagnostic code had an AMA test result in the Komodo database. As AMA could not be used in the definition of PBC, a claims-based analysis was used to identify PBC patients in claims data requiring 2 outpatient claims or 1 inpatient claim based upon a validated algorithm (Myers 2010). In addition to the claims criteria, evidence of UDCA use was required, which would further improve the positive predictive value of the claims-based algorithm.

All Komodo patients who met diagnostic and eligibility criteria (summarized in Figure 19) between 01 Jun 2015 and 31 Dec 2021 were considered for this study. Given the availability of different therapeutic options, the same inclusion and exclusion criteria were applied for both

cohorts to account for any potential bias due to physician's choice of treatment (i.e., channeling bias).

Figure 19: Study 405 – Patient Eligibility: Inclusion and Exclusion Criteria



*Indicates specific to OCA-treated group only.
HCC=hepatocellular carcinoma; PLT=platelets; PSC=primary sclerosing cholangitis; TB=total bilirubin

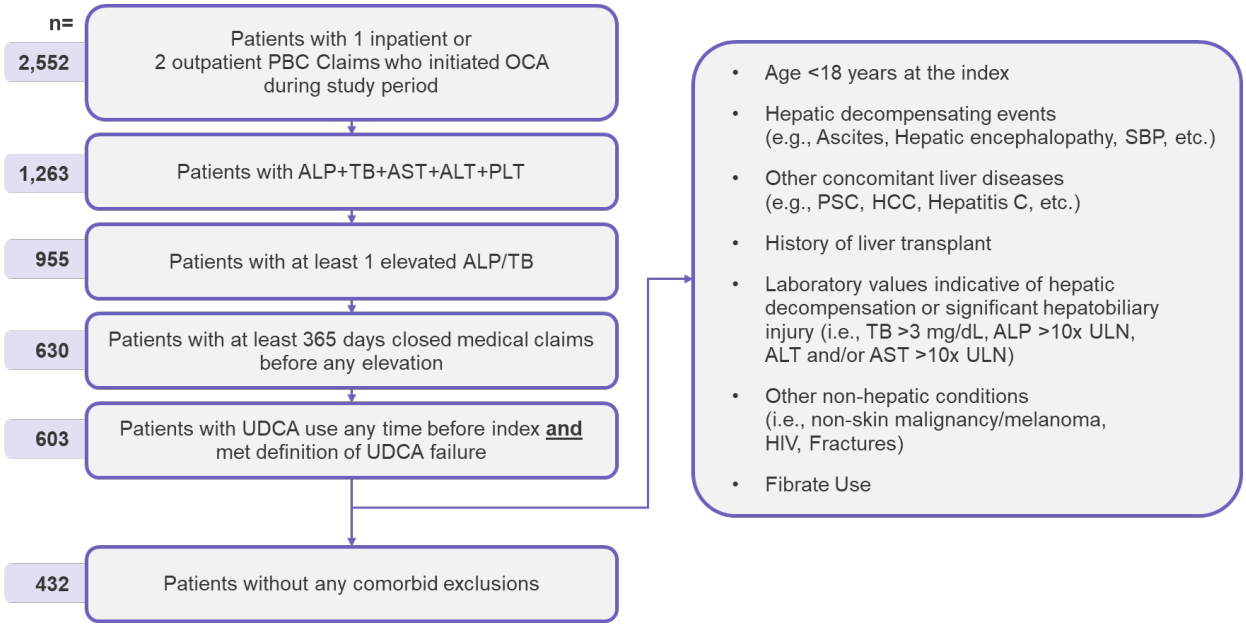
4.3.1.4. Cohort Identification

Cohort identification is summarized in Figure 20. A total of 143,197 patients had an inpatient or outpatient claim with an associated ICD9/10 code for PBC, of whom 97,648 had the requisite 1 inpatient claim or 2 outpatient claims (separated by at least 1 day).

Of the 97,648 patients with 1 inpatient claim or 2 outpatient claims:

- 2552 patients initiated OCA
- 1,263 patients had all 5 required laboratory values (ALP, AST, ALT, total bilirubin, and platelets)
- 955 patients had evidence of at least 1 total bilirubin and/or ALP elevation before or at the index
- 630 patients had closed medical claims data available for at least 365 days before an elevated ALP and/or total bilirubin level (62-day allowable gap)
- 603 patients had a documented history of UDCA use and met the prespecified criteria for UDCA failure (inadequate response, discontinuation, or intolerance)
- 432 patients did not have comorbid exclusions.

Figure 20: Study 405 – OCA-treated Patient Eligibility and Exclusions



OCA=obeticholic acid; PBC=primary biliary cholangitis; TB=total bilirubin; UDCA=ursodeoxycholic acid: PLT=platelets; PSC=primary sclerosing cholangitis; HCC=Hepatocellular Carcinoma; SBP= Spontaneous bacterial peritonitis

After application of the same inclusion/exclusion criteria to identify OCA eligible but non-OCA treated patients, 12,400 non-OCA indexes mapping to 4535 patients in the control group were identified. The patient attrition observed in Study 405 was similar to the attrition seen in other claims-based studies that leveraged RWE for regulatory decision making (e.g., Palbociclib (Ibrance) [Rugo 2022]).

After applying PBC diagnostic criteria and comorbid and contraindication exclusions, 432 of the 2552 patients in the OCA-treated group met all eligibility criteria specified for Study 405. A total of 2120 patients met the PBC claims-based definition of eligibility and had record of OCA initiation but did not meet other study inclusion criteria (including requirement of sufficient baseline laboratory data and 12-month continuous enrollment to establish inclusion/exclusion criteria or had comorbid exclusions). As shown in Table 5, baseline characteristics of the 2120 screen failed (OCA-treated excluded) patients were generally similar to the OCA-treated eligible patients with the exception that OCA-treated excluded patients had higher total bilirubin, consistent with the protocol-prespecified exclusion of more severe patients with comorbidities.

Table 5: Baseline Characteristics – OCA-treated Patients Excluded from Analysis vs. OCA-treated Study Patients

	OCA-Treated Excluded Patients N=2120	OCA-Treated Eligible Patients N=432
Age (years), Mean (SD)	57.2 (10.8)	56.3 (10.6)
Female, n (%)	1940.0 (91.5)	396.0 (91.7)
ALP (U/L), Mean (SD)	302.7 (215.1)	294.8 (155.5)
Missing, n (%)	1482 (69.9)	0
Total Bilirubin (mg/dL), Mean (SD)	1.2 (2.2)	0.7 (0.5)
Missing, n (%)	1470 (69.3)	4 (0.9)
Cirrhosis (Yes), n (%)	938.0 (44.2)	214.0 (49.5)

OCA=obeticholic acid

4.3.1.5. Propensity Score-based Weighting

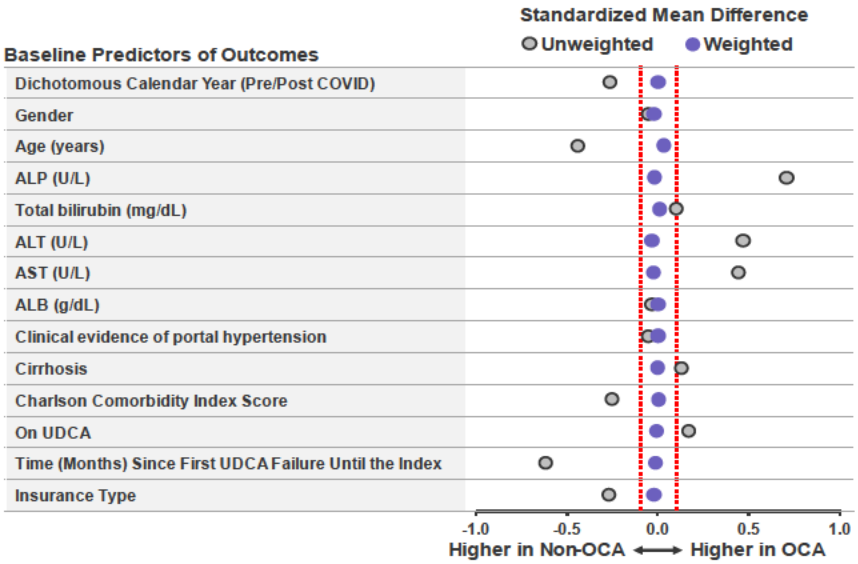
In the absence of randomization, a rigorous method was employed to ensure balance across treatments as follows:

1. Key baseline predictors of outcomes were pre-specified by an independent, expert Medical Team of gastroenterologists and hepatologists.
2. Pre-specified factors included pre/post coronavirus-19 (COVID) calendar year, gender, age, labs, clinical evidence of portal hypertension, cirrhosis, Charlson Comorbidity Index (CCI) - a validated measure encompassing major comorbidities including CV disease and cancers associated with survival, UDCA use, and insurance type.
3. Propensity score-based weighting was applied to adjust for differences in covariate distribution using standardized mortality/morbidity ratio (SMR) weights.

As shown in Figure 21, following propensity score weighting, the OCA and non-OCA-treated groups were well-balanced on the pre-specified key baseline predictors of outcomes. Variables fell within the prespecified standard mean difference thresholds of 0.1, indicating there was no substantial residual imbalance for any of the covariates after weighting.

Figure 21: Study 405 – Prespecified Prognostic Factors are Balanced After Weighting

- Baseline predictors prespecified by independent Medical Team
- Propensity score-based weighting addressed differences in covariate distribution
- SMR weights ensured balance between OCA and non-OCA groups



ALB=albumin; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; UDCA= ursodeoxycholic acid

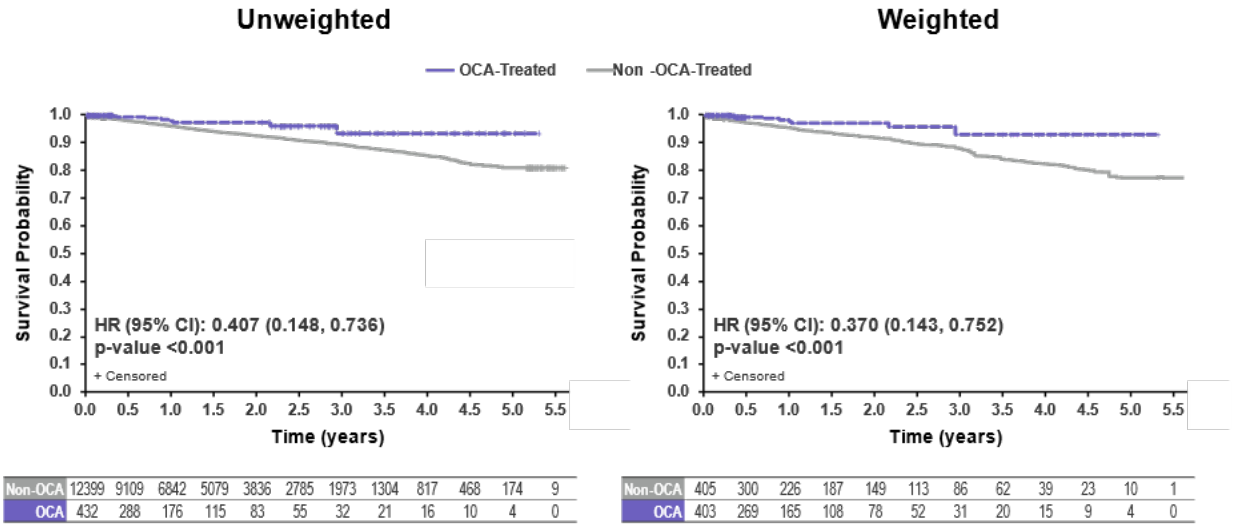
Before weighting, OCA-treated patients had a higher ALP, higher AST, higher ALT and higher proportion with cirrhosis all indicative of higher risk of adverse outcomes. After applying SMR weighting, there were 403 indices in the OCA-treated group with a mean follow up time of 14.3 months and 405 OCA eligible but non-OCA treated indices, with a mean follow up time of 20.6 months. Demographic and other baseline characteristics were similar between groups after weighting (see Appendix B, Section 8.2.3.4).

4.3.1.6. Primary Endpoint

Figure 22 shows the unweighted and weighted Kaplan–Meier curves for time to all-cause death, liver transplant, or hospitalization for hepatic decompensation by treatment group.

OCA treatment was associated with a clinically meaningful 63% reduction in the relative risk (HR=0.37; 95% CI: 0.14-0.75; p<0.001) of all-cause death, liver transplant, or hospitalization for hepatic decompensation among the OCA-treated group (event rate=8/403) compared to the weighted non-OCA-treated group (event rate=31.8/405.4). The unweighted analysis was consistent with these findings.

Figure 22: Study 405 – Time to First Occurrence of Hospitalization for Hepatic Decompensation, Liver Transplant, or Death (Unweighted and Weighted)



HR=hazard ratio; OCA=obeticholic acid

As shown on the left side of Figure 23, OCA's benefit was consistent across all three components of the primary endpoint. Fewer OCA-treated patients experienced hospitalization for hepatic decompensation, liver transplant, and death than non-OCA-treated patients.

As shown on the right side of Figure 23, modeling projects that treating 1000 patients with OCA for 5 years would prevent approximately 85 cases of hepatic decompensation, 16 liver transplants, and 43 deaths. This is substantial and clinically meaningful for a rare and serious disease such as PBC.

Figure 23: Study 405 – Demonstrates Benefit Across all Primary Endpoint Components

Study 405 Primary Efficacy Results	OCA Treated N 403	Weighted Non OCA Treated N 405.4	Estimated Number of First Events Avoided among modeled cohort of 1000 patients over 5 Years* with OCA Treatment
Primary Composite Endpoint, Hazard Ratio (95% CI)	0.37 (0.14, 0.75)		
Components of Primary Endpoint, n (%)			
Hospitalization for hepatic decompensation	6 (1.5)	23.0 (5.7)	**85**
Liver transplant	0 (0)	1.6 (0.4)	**16**
Death	2 (0.5)	7.2 (1.8)	**43**

OCA=obeticholic acid
*Modeled results based on primary composite endpoint event rates using 1,000 patients over a 5-year period.

4.3.1.7. Sensitivity Analyses

In the absence of randomization, there is the possibility that there could be unobserved variables with potential for residual, unmeasured confounding. A rigorous quantitative bias analysis was conducted to assess this possibility, using a range of assumptions for the prevalence of a potential confounder, and its association with both exposure and outcomes. Only an unmeasured confounder that is prevalent in at least half of the population *and* is highly associated with both exposure *and* outcomes negates the primary endpoint results. This is highly unlikely given that the natural history and prognostic factors associated with PBC are well understood. Therefore, this sensitivity analysis supports the robustness of the primary endpoint results (Appendix B, Section 8.2.3.5).

While an as-treated analysis is the standard approach for observational studies (i.e., censoring for OCA-treated patients 90 days after OCA discontinuation), an ITT analysis was run as a sensitivity analysis using 2 approaches:

- ITT approach 1: OCA indexes not censored after discontinuation
- ITT approach 2: OCA indexes not censored after discontinuation and control indexes:
  - Not censored at OCA initiation
  - Not censored at UDCA reinitiation (only for control indexes in which UDCA failure was defined by discontinuation)

Even under this scenario, a clinically meaningful benefit was observed:

- ITT 1 approach: HR 0.59, 95% CI: 0.34, 1.00
- ITT 2 approach: HR 0.64, 95% CI: 0.38, 1.05

Further details are in Appendix B, Section 8.2.3.6.

4.3.1.8. Limitations of Analyses of Real-World Data

There are inherent limitations to the analysis of RWD. For example, healthcare claims data can lack depth in the data captured, study cohorts are not randomized, and there is a potential for residual unmeasured confounding. Table 6 summarizes the key methodological attributes used in Study 405 to address these limitations (Table 6).

Table 6: Methodology Addresses Study 405 Limitations

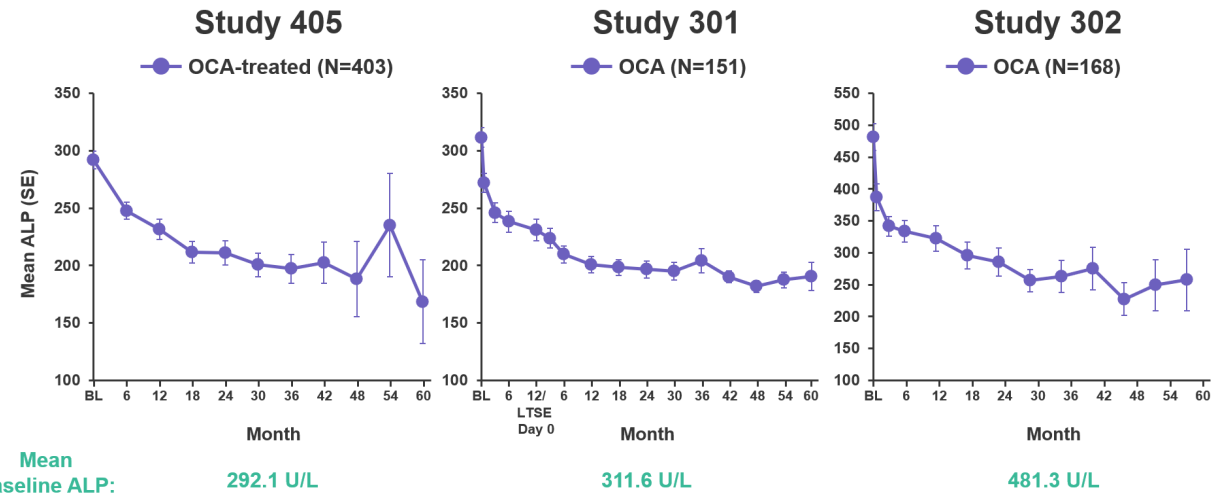
Real World Limitations	Strengths of Study 405
Claims database limited in depth of data collected	• Robust sample size for PBC (rare disease), including large number of patients treated with OCA in real-world clinical practice • Data from Komodo linked to other supplemental databases (laboratory, liver transplant, and vital status datasets) to enrich data collected from claims database • Hard endpoint of hospitalizations, liver transplants, and deaths well captured
Not randomized	• Propensity score-based SMR weighting ensured balance across cohorts
Potential for residual confounding	• Robust benefit even in the presence of residual confounding

OCA=obeticholic acid; PBC=primary biliary cholangitis; SMR=standardized mortality/morbidity ratio

4.3.1.9. Biochemical Marker Improvement

Study 405 demonstrated a benefit on ALP that was consistent with that observed in Studies 301 and 302. (Figure 24). Results were also consistent for ALT, AST and total bilirubin (Appendix B, Section 8.2.3.7).

Figure 24: OCA Demonstrated Significant and Clinically Meaningful Decreases in ALP Across Studies

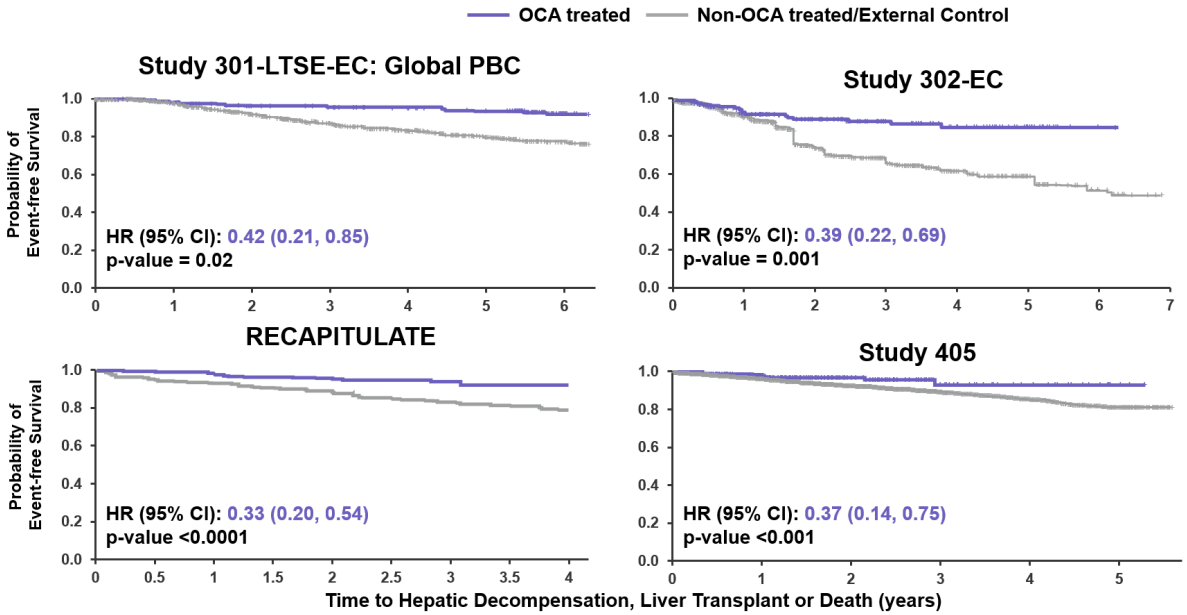


OCA=obeticholic acid

4.3.2. Other Supportive Real-World Evidence Studies

Despite the limitations and differences in capturing RWD across health claims databases and registries, there was a clinically meaningful, consistent improvement in event-free (58% to 67%; Figure 25) and transplant-free (60% to 71%; Figure 26) survival in patients treated with OCA compared to patients not treated on OCA across the different real-world studies (405, 301 EC, 302 EC, and the independent study RECAPITULATE).

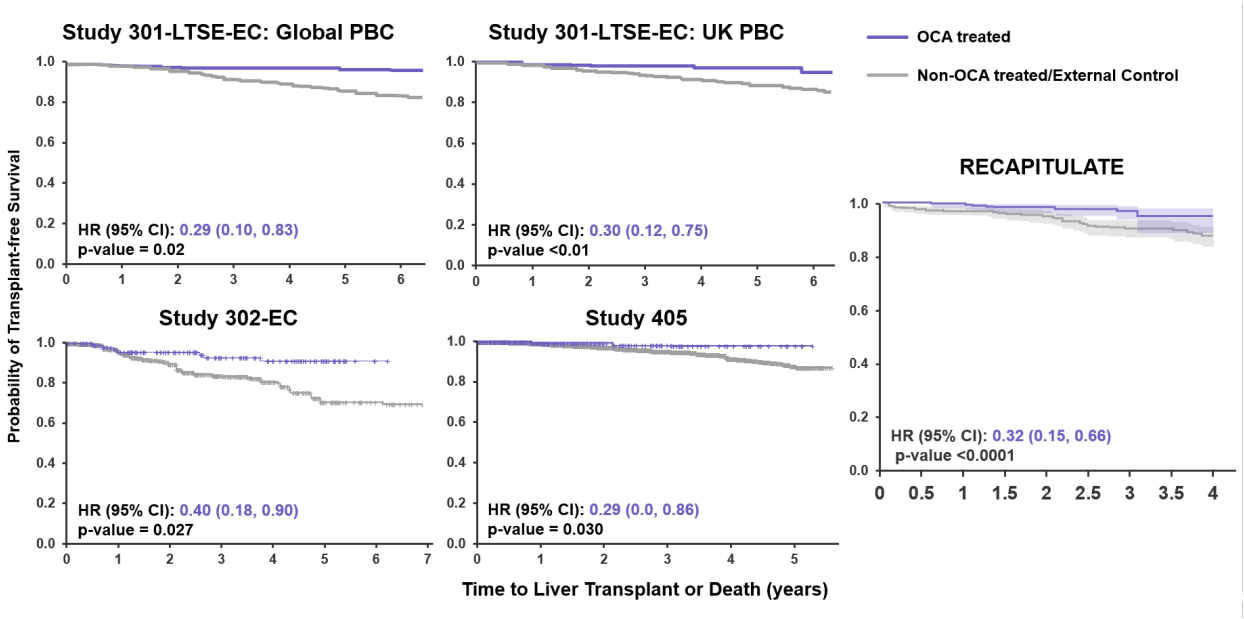
Figure 25: Consistent Impact on Event-free Survival (Hepatic Decompensation, Liver Transplant, or Death) Across RWE Studies



EC=external control; HR=hazard ratio; LTSE=long-term safety extension; OCA=obeticholic acid; PBC=primary biliary cholangitis; RWE=real-world evidence; UK=United Kingdom

Note: The UK-PBC registry excluded patients with hepatic decompensation at index and was not fit for purpose for event-free survival.

Figure 26: Consistent Impact on Transplant-free (Liver Transplant or Death) Survival Across RWE Studies



EC=external control; HR=hazard ratio; LTSE=long-term safety extension; OCA=obeticholic acid; PBC=primary biliary cholangitis; RWE=real-world evidence; UK=United Kingdom

4.3.3. Proposed Real-World Evidence Study 407

While it is Intercept's position that totality of evidence demonstrates benefit based on clinical outcomes, Intercept remains committed to generating additional RWE in patients with PBC treated with OCA and has recently submitted a proposal to the FDA outlining a real-world study (Study 407) to evaluate the effectiveness of OCA on clinical outcomes in patients with PBC without clinical evidence of portal hypertension. Electronic health record (EHR)-derived RWD sources will be evaluated to select fit-for-use data source(s) to answer the objectives of the study (US FDA 2018b). The abstracted data from the EHRs will include both structured data as well as unstructured narrative text including doctors' notes to strengthen quality and quantity of collected data. Data from patients with PBC in real-world settings can serve as alternative sources of information for long-term monitoring and analysis of OCA treatment, as OCA has been approved as a second-line treatment for the last 8 years. Study 407 proposes an EHR-based observational cohort study documenting clinical outcomes with primary objective defined as time-to-first occurrence of the composite endpoint of all-cause death, liver transplant, or hepatic decompensation. The proposed data source for Study 407 will also allow for capture of key safety events of interest following initiation of treatment. This study will follow a target trial emulation design. The study inclusion/exclusion criteria (UDCA failure definitions), treatment groups, outcomes, and censoring criteria as well as any critical variables (confounders, subgroups, covariates, or additional variables of interest) will be closely aligned to the Study 405.

4.4. Summary of the Totality of Evidence Supporting Efficacy

PMR Study 302 was designed to confirm benefit in an advanced population based on clinical outcomes for patients on OCA compared to patients not on OCA.

Per ITT principles, the design specified that patients who discontinued investigational product and remained in Study 302 continue to contribute to the primary efficacy analysis as randomized. In some cases, this included patients who began other active therapies such as commercial Ocaliva or unapproved second-line treatments for PBC (e.g., bezafibrate or fenofibrate).

Study 302 could not answer the primary efficacy research question due to the observed biases of functional unblinding (e.g., patients were unblinded to their ALP and used this information to stay or stop study participation) and treatment crossover (e.g., patients crossed over to commercial OCA or other active treatment based on knowledge of ALP levels). However, when adjustments are made to at least partially account for informative censoring and crossover to commercial OCA or other active therapies, post-hoc analyses show a shift towards a clinically meaningful benefit (HR [95% CI] 0.69 [0.50, 0.96]).

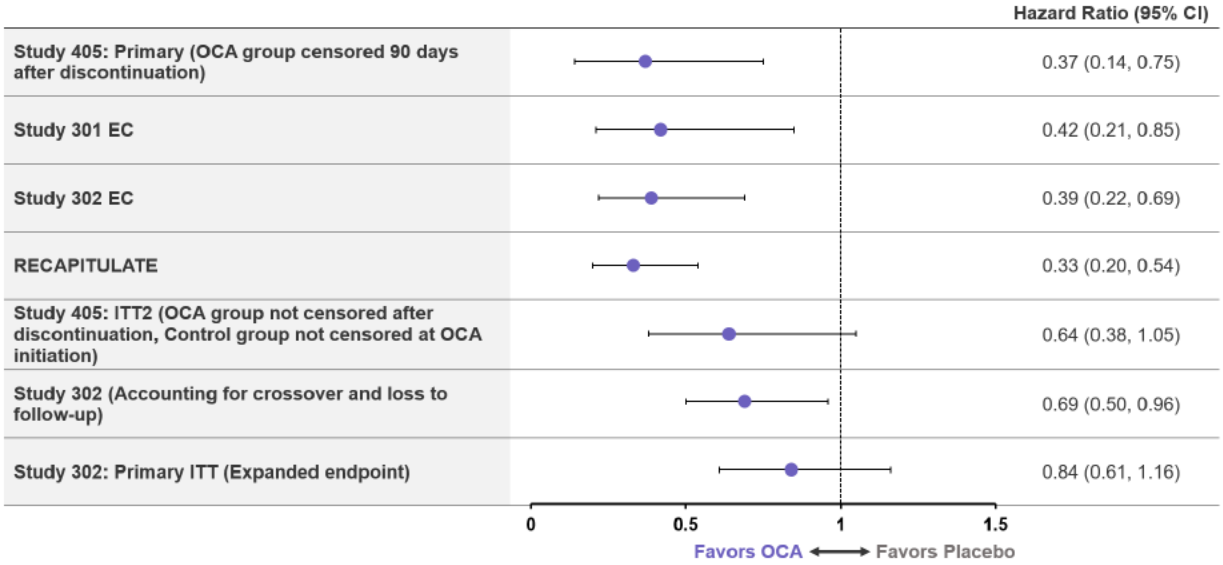
Substantial evidence of effectiveness was established in Study 405, including a clinically meaningful benefit on event-free survival and other clinical outcomes (HR [95% CI] 0.37 [0.14, 0.75]). Study 405 was an adequate and well-controlled trial that aligns to FDA RWE guidances, including key principles related to reliability and relevance. This study employed the "as-treated" analysis approach (i.e., censoring for OCA-treated patients 90 days after OCA discontinuation), which is conventionally used in observational studies for evaluating long-term benefit for a chronic therapy.

An ITT analysis (i.e., OCA indexes not censored after treatment discontinuation) was run as a sensitivity analysis in Study 405 and a clinically meaningful benefit was observed (HR [95% CI] 0.64 [0.38, 1.05]). This benefit was consistent with the comparable ITT sensitivity analysis for Study 302 (HR [95% CI] 0.69 [0.50, 0.96]).

The totality of evidence including Sponsor-supported and independent RWE-based studies provides consistent evidence of clinically meaningful OCA benefit in improving event-free and transplant-free survival in patients living with PBC with inadequate response or intolerant to UDCA (Figure 27).

In addition, the favorable and consistent improvement on key biomarkers of disease progression (e.g., ALP, GGT) across the entire clinical development program shows that OCA is continuing to impact the underlying disease pathophysiology of PBC.

Figure 27: Consistent Evidence of Clinically Meaningful Benefit of OCA on Event-free Survival (Death, Liver Transplant, or Hepatic Decompensation)



EC=external control; ITT=intent-to-treat; OCA=obeticholic acid
Control group=non-OCA-treated patients

5. SAFETY RESULTS

In patients with PBC, OCA was generally safe and well-tolerated, including long-term exposure across clinical studies including RWE and over 8 years of cumulative global postmarketing experience (>42,000 PYs of postmarketing safety surveillance). The most common AE was pruritus, which was generally mild to moderate in severity and managed with medication. Rates of discontinuation due to pruritus across clinical trials as well as real-world studies are low, at approximately 10% to 15%. Importantly, pruritus symptoms do not correlate with more advanced PBC disease stage or with clinical outcomes (Mayo 2008, Crosignani 2008).

In patients with PBC who are within the Ocaliva USPI indicated population (i.e., earlier stage disease), the risk for liver injury is low. Hepatic safety is managed with routine monitoring and drug interruption or discontinuation when indicated. Since the 2021 Ocaliva label update, reports of liver injury in the postmarketing setting are low with 0.03 events per 100 PYs. There is no evidence for excess risk of CV, dyslipidemia, gallbladder/gallstone, and renal AEs in patients with PBC across the clinical trial program, including RWE.

OCA has a well-characterized safety profile since its accelerated approval in 2016. Safety data include long-term exposure across clinical studies (Studies 301 and 302), RWE (Study 405) and 8 years of cumulative postmarketing experience (>42,000 PYs).

To minimize the impact of bias observed in the ITT population from Study 302 due to treatment crossover, safety analyses were performed using treatment-emergent events (TEAEs) up to

30 days after last dose of investigational product and censored for crossover to commercial Ocaliva.

5.1. Overview of Safety from Registration Study 301 (Double-Blind and LTSE)

Data from Study 301 established the initial safety profile of Ocaliva. During the 12-month, DB period of Study 301, no clinically meaningful differences were observed between the OCA and placebo groups for overall TEAEs, and administration of OCA 5 mg and OCA 10 mg was generally well tolerated (Appendix C, Section 8.3.3). The majority of TEAEs reported in the OCA groups were due to pruritus. TEAEs leading to study discontinuation were relatively low (7-11%) in the 12-month, DB phase and remained low (13%) over the 5-year LTSE period, including for pruritus.

5.2. Safety Topics of Interest

Since accelerated approval of Ocaliva in 2016, safety topics of interest including hepatic, CV, dyslipidemia, renal, gallbladder/gallstone-related, and pruritus events have been evaluated in the PBC clinical program.

In addition to the safety analyses summarized below, exposure-adjusted incidence rates (EAIRs) are also presented for each safety topic in clinical studies with a control group (Studies 301 Double-Blind, 302, and 405) in Appendix C, Section 8.3.5 and open-label Study 301 LTSE in Appendix C, Section 8.3.6.

5.2.1. Hepatic

Given the evolution in the understanding of hepatic safety for Ocaliva and the associated changes to the indicated population over the past several years, a comprehensive evaluation of hepatic events across all patients (including those patients with more advanced disease who are now contraindicated) was performed, including:

- Investigator-reported hepatic AEs in Studies 301, 302 and 405.
- Evaluation of drug-induced serious hepatotoxicity (eDISH) screening plots in Study 302.
- Adjudication of potential liver injury events based on a broad set of hepatic trigger events (AEs and pre-specified lab thresholds) to determine severity and causality by an independent drug-induced liver injury (DILI) committee (Hepatic Safety Adjudication Committee [HSAC]) in Study 302.
- Detailed individual case review in patients who are indicated per the current USPI based on baseline disease status from eDISH, adjudicated potential liver injury, and liver transplants and deaths assessments in Study 302.
- Postmarketing hepatic safety review.

Since Study 302 was initiated in 2015 and concluded in 2021 before the current USPI was fully implemented, the study included patients who would now be contraindicated at baseline. A USPI indicated population (i.e., with earlier stage disease; see Section 4.2.7 above) was identified retrospectively using baseline data. Although this analysis has limitations due to

incomplete availability of baseline data to correctly identify and exclude contraindicated patients (e.g., those with portal hypertension), the data show that 45% of patients in Study 302 would be considered indicated per the current USPI at baseline and 55% of patients enrolled in Study 302 would be contraindicated. In addition to the overall safety population in Study 302, hepatic safety analyses were conducted in the USPI indicated population.

Based on the totality of the hepatic safety analyses, the risk for liver injury was low in patients with PBC who were within the USPI indicated population. Hepatic safety continues to be manageable in the currently indicated population with routine monitoring and drug interruption or discontinuation in cases where liver injury is suspected.

5.2.1.1. Investigator-reported Hepatic Events

Across Studies 301, 302, and 405, there was no excess risk for investigator-reported hepatic AEs in OCA-treated patients compared to placebo (Table 7). In the USPI indicated population (i.e., subgroup of patients who met current USPI criteria) in Study 302, the incidence of hepatic AEs in the OCA group (27.2%) was lower than in the placebo group (42.6%; See Appendix C, Table 26 for more details).

Table 7: Investigator-reported Hepatic Adverse Events in Studies 301, 302, and 405 (Safety Population)

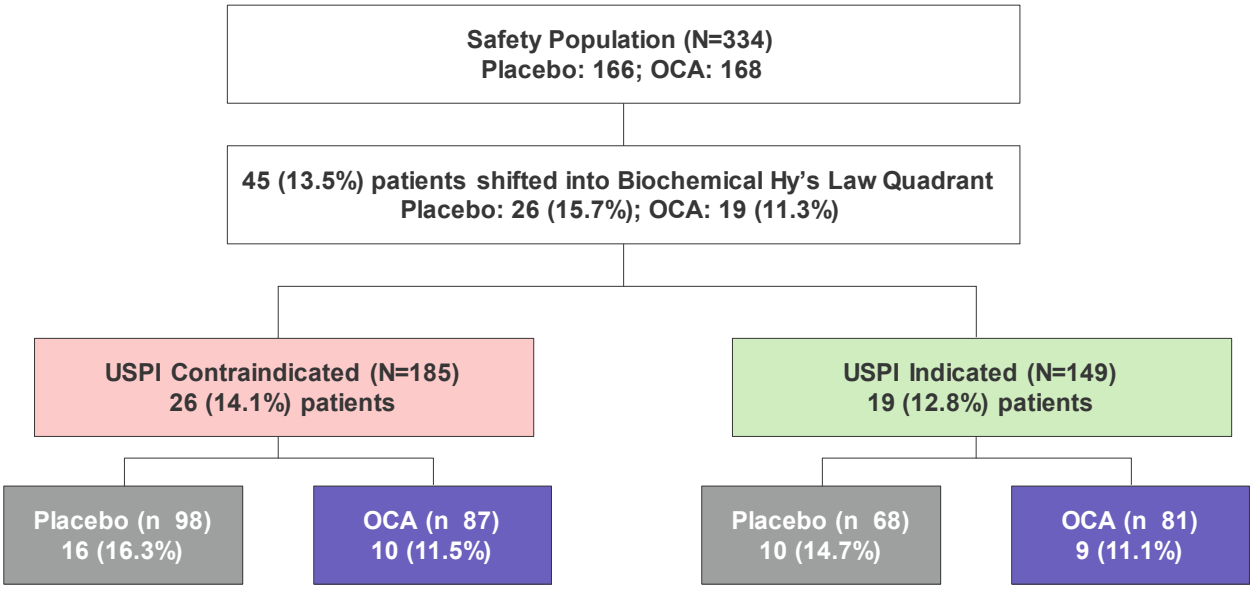
n (%)	Study 301 (Double-blind)			Study 302		Study 405	
	Placebo N=73	OCA 5→10 mg[a] N=70	OCA 10 mg N=73	Placebo N=166	OCA N=168	Weighted Non-OCA-treated N=405.4	Weighted OCA N=403
Hepatic TEAE	2 (2.7)	3 (4.3)	2 (2.7)	97 (58.4)	80 (47.6)	208.4 (51.4)	164 (40.7)
Serious AEs	1 (1.4)	1 (1.4)	0	16 (9.6)	15 (8.9)	47.6 (11.7)	27 (6.7)

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Note: In Study 405, serious AEs were defined as events that led to death and/or hospitalization.
[a] Patients randomized to the OCA titration treatment group received 5 mg OCA as their starting dose. Only OCA titration patients eligible for titration at Month 6 up-titrated to 10 mg OCA while patients ineligible for titration remained at their starting dose of 5 mg OCA.

5.2.1.2. Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) in Study 302

In Study 302, there was no imbalance between OCA and placebo groups in patients who experienced a shift (i.e., worsened) into the biochemical Hy's Law quadrant at peak lab excursions from baseline normal/near normal, Temple's corollary, or cholestasis quadrants: 19 (11.3%) patients in the OCA group and 26 (15.7%) patients in the placebo group (Figure 28; see Appendix C, Section 8.3.5.1.2 for eDISH definitions). Of these patients, 9 (11.1%) patients in the OCA group and 10 (14.7%) patients in the placebo group were within the current USPI indicated population at baseline.

Figure 28: Study 302 – eDISH Shifts into Hy's Law Quadrant: USPI Indicated versus USPI Contraindicated Population (Safety Population, N=334)



eDISH=evaluation of drug-induced serious hepatotoxicity; ITT=intent-to-treat; OCA=obeticholic acid; PH=portal hypertension; USPI=United States Prescribing Information

Note: Data presented are patients who were in the normal/near normal, Temple's corollary, or cholestasis range at baseline and shifted into the biochemical Hy's Law quadrant. Data do not include patients who were in biochemical Hy's Law at baseline and stayed in the biochemical Hy's Law quadrant: 6 (3.6%) patients in the OCA group and 9 (5.4%) patients in the placebo group; See Appendix C, Table 27.

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

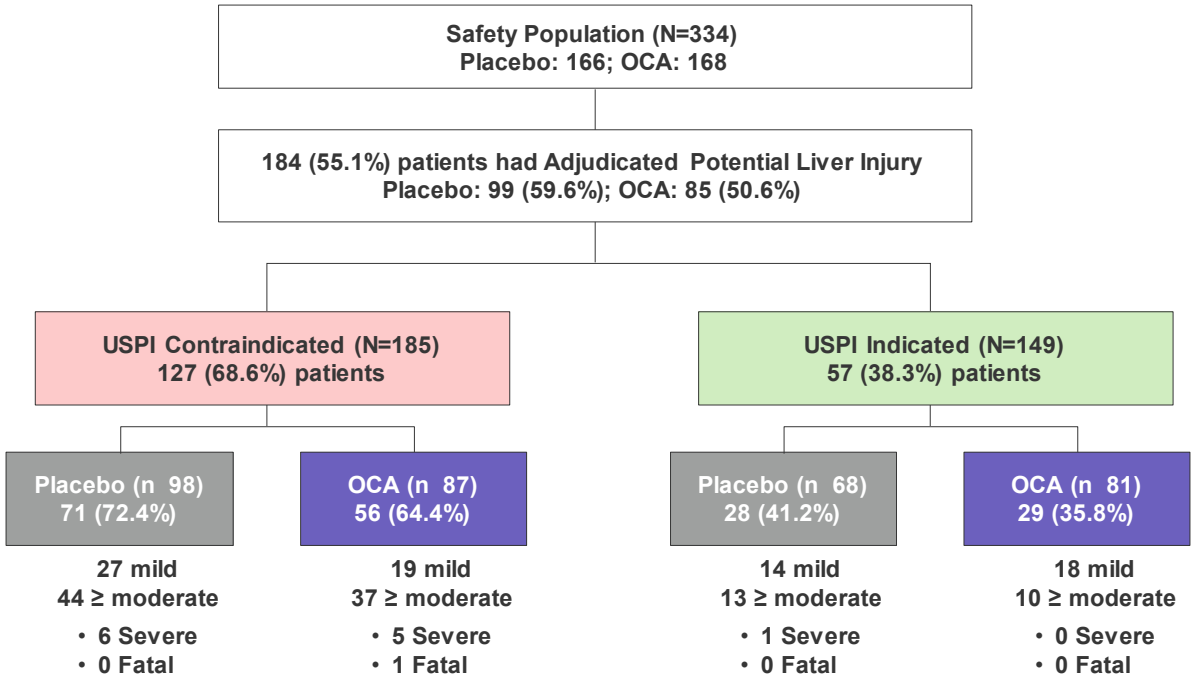
5.2.1.3. Adjudicated Potential Liver Injury Events in Study 302

In Study 302, a total of 184 patients experienced hepatic trigger events (based on Investigator-reported TEAEs and pre-specified lab thresholds) that met criteria for potential liver injury as assessed by the DILI committee (HSAC; 85 patients in the OCA group and 99 patients in the placebo group; Figure 29). Details of the adjudication process are described in Appendix C, Section 8.3.5.1.3.

The majority of patients who had a potential liver injury event were in the contraindicated population (69%) and would not be eligible to receive Ocaliva in current clinical practice. As expected, the incidence of adjudicated hepatic safety events was higher in the contraindicated population compared to the USPI indicated population for both the OCA and placebo groups, indicating risk of liver injury to be associated with disease severity.

In the USPI indicated population, the number of patients with potential liver injury events was balanced between the OCA and placebo groups, and the majority of potential liver injury events were mild or moderate in severity. No patients in the OCA group and 1 patient in the placebo group experienced an event considered severe by the HSAC, and there were no adjudicated liver injury events with a fatal outcome.

Figure 29: Study 302 – Adjudicated Hepatic Safety Events: USPI Indicated versus USPI Contraindicated Population



OCA=obeticholic acid; USPI=United States Prescribing Information

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

Upon adjudicating for causality, a total of 5 patients in the USPI indicated population had a potential liver injury event assessed as possibly related to investigational product by the HSAC (4 patients in the OCA group and 1 patient in the placebo group; Table 8). See Appendix C, Figure 39, Figure 40, Figure 41, Figure 42, and Figure 43 for patient narratives.

These events occurred within the first 3 to 4 months of starting investigational product and were appropriately managed with discontinuation of investigational product and any confounding hepatotoxic medications such as rifampicin. All events resolved or returned to baseline status. No events were assessed as probably or highly likely related to investigational product by the HSAC.

Table 8: Study 302 – Summary of Possibly Related Potential Liver Injury in the USPI Indicated Population

Patient/ Treatment	Country	HSAC Causality/ Severity	Confounders	Lab Observations	Onset Study Day	Base/ Peak ALT (U/L)	Base/ Peak AST (U/L)	Base/ Peak ALP (U/L)	Base/ Peak TB (mg/dL)	Intervention	Outcome
OCA1 69-yr Female OCA	Argentina	Possible/ **Mild**	PBC disease progression	Fluctuating high ALP	Day 91	17 / 27	22 / 23	543 / 1128*	0.3 / 0.5	DC OCA (Day 241) Negative dechallenge	Liver labs at baseline by EOS
OCA2 41-yr Female OCA	Chile	Possible/ **Mild**	Celiac disease (Day 462)	AST/ALT transient elevation	Day 92	136 / 313	99 / 264	488 / 466	0.8 / 1.1	None; continued OCA	Resolved (Day 114)
OCA3 45-yr Female OCA	Netherlands	Possible/ **Moderate**	Gallstones (Day 24)	AST/ALT/TB elevation	Day 80	185 / 764	85 / 378	574 / 479	1.0 / 4.9	DC OCA (Day 87) Cholecystectomy (Day 121)	Resolved (Day 139)
OCA4 57-yr Female OCA	Germany	Possible/ **Moderate-severe**	Rifampicin (Started Day 16)	AST/ALT elevation	Day 85	87 / 680	90 / 791	585 / 567	1.4 / 1.2	DC Rifampicin (Day 90) DC OCA (Day 93)	Resolved (Day 126)
PBO1 44-yr Female Placebo	Turkey	Possible/ **Moderate**	Rifampicin (Started Day 87)	AST/ALT/ALP/GGT/ TB elevation	Day 104	109 / 136	108 / 133	426 / 537	1.4 / 2.5	DC PBO (Day 107) DC Rifampicin (Day 118)	Undetermined

BL=baseline; DC=discontinued; EOS=end of study; HSAC= Hepatic Safety Adjudication Committee; OCA=obeticholic acid; PBC= primary biliary cholangitis; TB=total bilirubin; ULN=upper limit of normal; USPI=United States Prescribing Information

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

Note: Peak lab values shown here correspond to lab value peaks at time of onset of potential liver injury.

*The corresponding ALP ULN is 300 U/L for the peak ALP at onset for patient OCA1 (baseline ALP value corresponds to an ALP ULN of 123 U/L).

5.2.1.4. Review of Hepatic Cases in the USPI Indicated Population in Study 302

A comprehensive patient level review of hepatic cases of highest importance within the USPI indicated population was performed based on the following assessments:

- eDISH screening plots: to include patients who shifted into the biochemical Hy's Law quadrant from baseline
- DILI committee (HSAC) adjudication: to include potential liver injury cases adjudicated by the independent committee with at least moderate severity not already identified from eDISH screening
- Patients with extreme labs values on eDISH screening plots not already identified by Hy's Law shift analysis or DILI adjudication

A total of 14 (9.4%) patients within the USPI indicated population (N=149) were identified as cases of highest importance (10 [12.3%] of the 81 patients in the OCA group and 4 [5.9%] of the 68 patients in the placebo group).

Of the 10 patients in the OCA group identified for patient level review, 3 (3.7%) patients remained indicated per the USPI throughout the study (i.e., did not develop a contraindication; Table 9):

- Patient OCA3 (45-year-old White Female) diagnosed with cholelithiasis on Day 49, had a potential liver injury event on Day 80 (as discussed in Figure 41), which resolved by Day 139 with discontinuation of OCA and after cholecystectomy.
- Patient OCA4 (57-year-old White Female) had a potential liver injury event on Day 85 (as discussed in Figure 42), which resolved by Day 126 with discontinuation of OCA and other confounding hepatotoxic medications (rifampicin).
- Patient OCA5 (70-year-old White Female) died due to a subdural hematoma after a fall while walking in the rain; assessed as unlikely related to investigational product.

Of the remaining patients in the OCA group, 6 (7.4%) patients continued OCA months to years after developing a contraindication during the study and 1 (1.2%) patient, while classified as on-label at baseline programmatically, was likely contraindicated at baseline based on patient-level review (See Figure 45 for more details). These 7 patients would have stopped treatment or should not have initiated treatment per the current USPI (Table 10). However, since Study 302 was conducted before the 2021 USPI was fully implemented, these patients remained on OCA and experienced hepatic events well after developing a contraindication.

Of the 4 patients in the placebo group, 1 patient (Patient PBO1, as discussed in Figure 43) did not develop a contraindication during the study and had a potential liver injury event on Day 104 that was considered possibly related by the HSAC. The patient dropped out of the study after the event with no further follow-up. The remaining 3 patients in the placebo group developed contraindications during the study (Table 10).

Within the USPI indicated population, an additional 4 patients had a liver transplant or death without evidence of hepatic injury (Table 11). Therefore, these 4 cases are not included in the 14 hepatic cases of highest importance presented in Table 9 and Table 10. Throughout the study, these 4 additional patients remained in the normal/near normal quadrant on eDISH screening plot and/or did not experience a potential liver injury event adjudicated by the independent DILI committee (HSAC).

Based on the comprehensive hepatic assessment, the risk of hepatic events associated with Ocaliva is low, and events occurring in the current USPI indicated population are monitorable and reversible per the current USPI guidance (Appendix E, Section 8.5). The majority of OCA-treated patients who either shifted into Hy's Law, had a possibly related and at least moderate potential liver injury event, and/or had a liver transplant or death would no longer be eligible for treatment per the current USPI. However, since Study 302 was conducted before the 2021 USPI was implemented, many of these patients continued study drug well after developing contraindications.

Table 9: Study 302 - Hepatic Review of Cases in the USPI Indicated Population who Remained Indicated per 2021 USPI

Patient/ IP	Country	IP D/C (Study Day)	Adjudicated Event (Study Day)	Adjudicated Severity/ Causality	Confounders	Intervention	Comment
OCA3 45-yr Female/ OCA	Netherlands	87	Hepatocellular injury (80)	Possibly related/ Moderate	Gallstones	DC OCA (Day 87) Cholecystectomy (Day 121)	Resolved (Day 139)
OCA4 57-yr Female/ OCA	Germany	93	Hepatocellular injury (85)	Possibly related/ Moderate-severe	Rifampicin	DC Rifampicin (Day 90) DC OCA (Day 93)	Resolved (Day 126)
OCA5 70-yr Female/ OCA	US	221	Non-liver related death (618)	Unlikely related/ Fatal	N/A	N/A	Subdural hematoma due to a fall
PBO1 44-yr Female/ Placebo	Turkey	107	Mixed pattern injury (104)	Possibly related/ Moderate	Rifampicin	DC Placebo (Day 107) DC Rifampicin (Day 118)	Undetermined; patient withdrew consent

D/C=discontinuation; IP=investigational product; N/A=not applicable; OCA=obeticholic acid; USPI=United States Prescribing Information

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

Table 10: Study 302 - Hepatic Review of Cases in the USPI Indicated Population who Became Contraindicated per 2021 USPI During the Study

Patient/ IP	Country	IP D/C (Study Day)	Contraindication (Study Day)	Adjudicated Event (Study Day)	Adjudication Causality	Confounders	Time from IP D/C to Event	Time from Contra-indication to Event
OCA6 43-yr Female/ OCA	Denmark	199	Portal hypertension (0)	Liver transplant (639)	Possibly	Alcohol-use disorder, insulin-dependent DM, chronic pancreatitis, rifampicin	1.2 years	1.8 years
OCA7 49-yr Male/ OCA	Canada	912	Portal hypertension (365)	Liver Transplant (1580)	Unlikely	Long-standing ulcerative colitis, advanced fibrosis	1.8 years	3.3 years
OCA8 44-yr Female/ OCA	Denmark	593	Portal hypertension (365)	Liver Transplant (1356)	Unlikely	Rifampicin	2.1 years	2.7 years
OCA9 40-yr Female/ OCA	Canada	611	Hepatic impairment (597)	Liver Transplant (1412)	Unlikely	Plaquenil and NSAIDs	2.2 years	2.2 years
OCA10 43-yr Female/ OCA	US	667	Progression to CP-B8 (171)	Liver Transplant (812)	Unlikely	Rifampicin and fenofibrate	145 days	1.8 years
OCA11 43-yr Female/ OCA	Switzerland	434	Hepatic impairment (224)	Liver transplant (823)	Unlikely	D/C OCA due to pruritus	1.1 years	1.6 years

Patient/ IP	Country	IP D/C (Study Day)	Contraindication (Study Day)	Adjudicated Event (Study Day)	Adjudication Causality	Confounders	Time from IP D/C to Event	Time from Contra-indication to Event
OCA12 42-yr Female/ OCA	Argentina	889	Portal hypertension (377)	Liver-related Death (937)	Unlikely	Variceal bleed; ischemic cerebral injury	48 days	1.5 years
PBO2 48-yr Female/ Placebo	US	360	Hepatic impairment (92)	Progression to CP-B7 (179)	Possibly	Disease progression	--	87 days
PBO3 47-yr Female/ Placebo	United Kingdom	268	Portal hypertension (174)	Liver Transplant (1078)	Unlikely	Low platelets at baseline, D/C PBO Day 268 and initiated commercial OCA, D/C commercial OCA on Day 982	96 days	2.5 years
PBO4 40-yr Female/ Placebo	Sweden	179	Hepatic impairment (179)	Progression to CP-B9 (177)	Unlikely	Disease progression	--	--

CP=Child-Pugh; IP=investigational product; D/C=discontinued; DM=diabetes mellitus; N/A=not applicable; NSAID=non-steroidal anti-inflammatory drugs; OCA=obeticholic acid; US=United States; USPI=United States Prescribing Information

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

Table 11: Study 302 – Liver Transplants and Deaths in the USPI Indicated Population Not Included in Hepatic Case Summary

Patient	Country	IP D/C (Study Day)	Adjudicated Event (Study Day)	Time from Contraindication to Event	Adjudication Causality	Confounders
OCA13 69-yr Female/ OCA	US	296	Non-liver-related Death (317)	N/A	Unlikely	Stage IV B-Cell Lymphoma
OCA14 46-yr Female/ OCA	Argentina	223	Non-liver-related Death (887)	N/A	Unlikely	*C. difficile* colitis, multi-organ failure
OCA15 58-yr Female/ OCA	Denmark	221	Liver Transplant (234)	N/A	Unlikely	Severe pruritus w/ prior experimental MARS therapy at baseline, elective liver transplant w/ MELD score of 6
PBO5 53-yr Female/ Placebo	Argentina	379	Non-liver-related Death (512)	N/A	Unlikely	Paraplegia post-surgery for hip fracture

MARS=molecular adsorbent recirculation system
Note: Data presented occurred on-study.

5.2.1.5. Postmarketing Hepatic Safety

Since the revision of the USPI indication in May 2021, a marked decrease in the estimated reporting rates for fatal and hepatic events after the USPI label update was observed (Table 12). This decrease is likely a result of contraindicating Ocaliva therapy in patients with more advanced PBC who are at a higher risk for adverse outcomes. In addition, reports of liver injury in the postmarketing setting were low with 0.03 events per 100 PYs. Hepatic safety continues to be manageable in the currently indicated population with routine monitoring and drug interruption or discontinuation.

Table 12: Global Reporting Rates for Hepatic Events per 100 Patient Years Pre- and Post- USPI Update

	Pre-2021 USPI Update (~20,000 PY)	Post-2021 USPI Update (~25,000 PY)
All hepatic AEs	11.57	6.99
Serious hepatic AEs	3.80	1.61
Liver injury	0.08	0.03
Liver transplant	0.30	0.10
Fatal (all-cause) AEs	1.63	0.69
Fatal hepatic AEs	0.26	0.03

AE=adverse event; OCA=obeticholic acid; PBC=primary biliary cholangitis; PY=patient-years; USPI=United States Prescribing Information

Notes: Postmarketing reporting data cutoff date of March 2024. Estimates of postmarketing exposure are based on sales distribution data. Each unit (bottle) of OCA contains 30 tablets and is assumed to be prescribed at one tablet per day for one patient. It is not known whether these are patients newly initiating therapy or continuing therapy. Therefore, data are converted to an estimate of PYs (total units*30 days per unit/365.25 days per year).

It is important to note that unlike usual postmarketing reports, which are spontaneous (self-reported), the majority of postmarketing reports in the US for Ocaliva are derived from solicited reports from specialty pharmacies and the patient support program (InterConnect® Support Services). This important distinction allows for a meaningful assessment of OCA's safety profile in clinical practice and is not impacted by waning of self-reports over time, a phenomenon generally associated with postmarketing data. Intercept's postmarketing data are also reconciled against the FDA AE Reporting Systems (FAERS) database on a quarterly basis.

Overall, these results support demonstration of a positive impact from the 2021 USPI update for the safe use of Ocaliva in the appropriate patient population.

Intercept continues to monitor these topics through routine pharmacovigilance activities.

5.2.1.6. Risk Mitigation and Management

There are multiple layers of risk mitigation and management of hepatic safety, starting with the USPI. In addition to providing contraindications, the USPI provides guidance on monitoring for disease progression and management of OCA.

Ocaliva USPI for Patient Management:

Routinely monitor patients for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessments to determine whether drug discontinuation is needed.

Closely monitor patients with compensated cirrhosis, concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or with severe intercurrent illness for new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) or increases above the upper limit of normal in total bilirubin, direct bilirubin, or prothrombin time to determine whether drug discontinuation is needed.

Permanently discontinue OCALIVA in patients who:

- *develop laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy)*
- *have compensated cirrhosis and develop evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)*
- *experience clinically significant hepatic adverse reactions*
- *develop complete biliary obstruction*

If severe intercurrent illness occurs, interrupt treatment with OCALIVA and monitor the patient's liver function. After resolution of the intercurrent illness, consider the potential risks and benefits of restarting OCALIVA treatment.

Three additional layers of protection include:

- Specialty prescribers: Patients with PBC who have failed first-line therapy are at increased risk for progressive liver disease and its complications. These patients are managed by specialty practices (i.e., gastroenterology and hepatology). Specialists assess patients for eligibility of Ocaliva treatment, specifically excluding patients with compensated cirrhosis with evidence of portal hypertension, decompensated cirrhosis, or a prior decompensation event.
- Specialty pharmacies: In the US, Ocaliva is generally only available from a limited network of 6 specialty pharmacies. Payers manage access to Ocaliva through prior authorization, which requires submission of laboratory results and provider attestation that patients do not meet any of the contraindications per the current USPI. In addition, periodic re-authorization is required for patients to continue on Ocaliva.
- InterConnect: Intercept offers a patient support program for Ocaliva called InterConnect® Support Services. Enrollment into the InterConnect program requires that providers attest that patients do not meet any of the contraindications for Ocaliva. InterConnect enrollment is separate and distinct from payer policies and prior authorization for all patients.

Together, these layers of protection ensure the safe use of Ocaliva in the appropriate patient population.

5.2.2. Cardiovascular

The totality of data across clinical studies does not support an excess CV risk associated with OCA. The incidence of CV AEs in Studies 301 and 405 was generally similar across treatment groups (Table 13). While there was an imbalance observed in crude incidence in Study 302, no meaningful difference in Major Adverse CV Events (MACE) was observed between OCA and placebo (5 patients in the OCA group and 3 patients in the placebo group) based on independent adjudication of all suspected MACE, including CV-related death, non-fatal myocardial infarction, non-fatal stroke, and additional CV events by an expert committee in a blinded fashion (Cardiac Outcomes Committee). See Appendix C, Section 8.3.5.2.2 for more details on the adjudicated CV events.

Table 13: Investigator-reported Cardiovascular Events in Studies 301, 302, and 405 (Safety Population)

	Study 301 (Double-blind)			Study 302		Study 405	
n (%)	Placebo N=73	OCA 5→10 mg N=70	OCA 10 mg N=73	Placebo N=166	OCA N=168	Weighted Non-OCA-treated N=405.4	Weighted OCA N=403
CV TEAE	0	0	1 (1.4)	7 (4.2)	16 (9.5)	52.8 (13.0)	37 (9.2)
Serious AEs	0	0	0	3 (1.8)	7 (4.2)	12.3 (3.0)	8 (2.0)

AE=adverse event; CV=cardiovascular; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Note: For Study 405, serious AEs were defined as events that led to death and/or hospitalization.

5.2.3. Pruritus

Pruritus is a known manifestation of PBC with approximately 74% of patients reporting pruritus at some point during their diagnosis and 35% reporting persistent symptoms (Hegade 2019). Pruritus is a known adverse drug reaction for Ocaliva since accelerated approval in May 2016. Investigator-reported pruritus events across studies are summarized in Table 14.

Pruritus symptoms are mostly mild to moderate and are well managed by clinicians experienced in the management of patients with PBC, and with clear guidance provided in the Ocaliva USPI. Rates of discontinuation due to pruritus across clinical trials as well as real-world studies are low, at approximately 10% to 15%. Further, the overall treatment persistence rate in the open-label, long-term study (Study 301 LTSE) was approximately 78% following 4 years of treatment. This is also supported by treatment adherence analyses from real world clinical practice data for Ocaliva with an annual retention rate of 78% to 80% (Patel 2022, Gibbons 2022), which are similar to other chronic therapies such as adherence to antidiabetic medications or statins.

Lower rates of pruritus for both OCA treated and non-OCA treated patients in Study 405 are expected since pruritus is not generally a serious clinical event requiring a clinic visit; hence has a lower rate of capture in a health claims data source.

Table 14: Pruritus Events in Studies 301, 302, and 405

n (%)	Study 301 (Double-blind)			Study 302		Study 405	
	Placebo N=73	OCA 5→10 mg N=70	OCA 10 mg N=73	Placebo N=166	OCA N=168	Weighted Non-OCA-treated N=405.4	Weighted OCA N=403
Pruritus TEAE	28 (38.4)	39 (55.7)	51 (69.9)	85 (51.8)	133 (79.2)	44.9 (11.1)	41 (10.2)
Serious AEs	0	0	0	0	2 (1.2)	5.3 (1.3)	0

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Note: For Study 405, serious AEs were defined as events that led to death and/or hospitalization and rates are generally lower because the source is claims data.

5.2.4. Additional Safety Events of Interest

There was no excess risk in dyslipidemia, gallbladder/gallstone, and renal events evaluated across clinical studies (Appendix C, Section 8.3.5.3, Section 8.3.5.5 and Section 8.3.5.6).

5.3. Summary of Safety

Based on the totality of data across clinical trials, including RWD, there is no evidence of excess risk for CV, dyslipidemia, gallbladder/gallstone, or renal events in OCA-treated patients compared to placebo. The most common AE was pruritus, which was generally mild to moderate in severity and managed adequately. The risk for liver injury is low in the current USPI indicated population (i.e., earlier-stage disease only).

In May 2021, the USPI was updated to contraindicate patients with more advanced disease, including patients with hepatic decompensation and patients with clinical evidence of portal hypertension. A patient-level review in Study 302 was conducted in the USPI indicated population, which showed that hepatic safety was manageable with routine monitoring and drug interruption or discontinuation when indicated.

Additionally, since the 2021 USPI update, the cumulative postmarketing experience has shown a significant decrease in the incidence of hepatic decompensation events including fatal events and with no new safety signals observed. The USPI and standard of care practice allows for monitoring and management of patients for evidence of toxicity or progression to contraindications per the USPI. Since Ocaliva is administered as second-line therapy, specialty pharmacies require extra processes to ensure only appropriate patients receive treatment.

6. BENEFIT-RISK FRAMEWORK

A benefit-risk assessment of Ocaliva in patients with PBC is provided in Table 15.

Table 15: Benefits and Risks Assessment

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PBC is a rare, serious, life-threatening, cholestatic liver disease with a complex autoimmune pathophysiology and well-understood natural history. • US prevalence is 105,000 adults (Buchanan-Peart 2023) • PBC primarily affects women between the ages of 40 and 60 (Trivella 2023). • The most common presenting symptoms are pruritus and fatigue. • Without intervention, 25% of patients will progress to liver failure within 10 years (EASL 2017). • Elevations in ALP and other liver biochemistries are reflective of the underlying hepatic disease pathology. • ALP is a biochemical marker that has been shown to significantly predict risk of death, liver transplant, and hepatic decompensation (Carbone 2013, Lammers 2014).	• PBC is a rare, serious, and progressive liver disease with a well-understood natural history that can progress to liver transplant and death. • The role of ALP as a predictor of risk is well-understood by patients and physicians.
Current Treatment Options	• First line: – UDCA: approximately 40% experience treatment failure and another 5% are intolerant • Second-line: – Ocaliva: the only FXR agonist available for PBC and the only second-line option with proven, long-term outcomes over 8 years of postmarketing experience (>42,000 patient years of exposure) – Elafibranor: PPAR with accelerated approval based on improvement in ALP, a surrogate endpoint – Seladelpar: PPAR under review by FDA • Off-label treatments: fibrates	• There is a continued unmet need for second-line therapies with multiple mechanisms of action. • Ocaliva is the only FXR agonist available for second-line treatment of PBC and its mechanism of action is complementary to both UDCA and PPARs. • Ocaliva is the only second-line option with long term outcomes based on real world experience.

	Evidence and Uncertainties	Conclusions and Reasons
Benefits	• Although Study 302 was designed and conducted as a randomized placebo-controlled trial, functional unblinding (due to patient knowledge of ALP) and treatment crossover to commercial therapy introduced bias in the pre-specified ITT analysis. Therefore, the ITT analysis was not able to answer the primary objective. However, post hoc analyses to adjust for treatment cross-over and informative censoring shift towards clinically meaningful benefit. • Study 405 is an adequate and well-controlled non-interventional study that shows a clinically meaningful, 63% reduction in the relative risk for the composite outcome of all-cause death, liver transplant or hospitalization for hepatic decompensation in the OCA-treated group compared to the non-OCA-treated group. • Supportive data from other real-world studies replicate this benefit and biomarker data from Studies 301, 302, and 405 are also consistent and favorable.	• Ocaliva continues to demonstrate a survival benefit in the currently indicated population (adults with PBC without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension [i.e., current USPI indicated population]). • Ocaliva demonstrates a reduction in serious and life-threatening outcome events compared to untreated patients in this population.
Risks and Risk Management	• Risk for liver injury is low in patients with earlier stage PBC who are indicated per the current USPI, and manageable with monitoring via routine labs and/or drug interruption or discontinuation in the appropriate clinical setting. • Based on totality of data, there is no evidence of excess risk for CV, dyslipidemia, gallbladder/gallstone, or renal events in OCA-treated patients compared to placebo. • Safety profile is well-characterized across clinical studies including RWE and extensive postmarketing experience from over 8 years of exposure (>42,000 PYs). • Current Ocaliva USPI guidance and standard of care practice allows for monitoring and management of patients for evidence of toxicity or progression to contraindications per the USPI. Since Ocaliva is administered as second-line therapy, specialty pharmacies require extra processes to ensure only appropriate patients receive treatment.	• The 2021 USPI update reflects the right patient population for Ocaliva (i.e., patients with earlier stage disease who have failed UDCA and remain at risk for adverse outcomes). • The risks of Ocaliva are well-known and monitored through routine pharmacovigilance, as guided by the USPI.

	Evidence and Uncertainties	Conclusions and Reasons
Summary of Benefit-Risk The benefit-risk of Ocaliva remains positive in the current USPI indicated population (i.e., patients without cirrhosis and with no clinical evidence of portal hypertension), who are at high risk for disease progression because of UDCA incomplete response. Ocaliva continues to fill a critical unmet need for second-line therapies through its unique mechanisms of action targeting fibrosis, cholestasis, and inflammation, and is the only second-line therapy in PBC to demonstrate survival improvement through a reduction in liver-related events and reductions in liver transplant and death in RWE observational studies and supporting analyses. The totality of evidence from Studies 301, 302, and 405 shows a clear benefit of Ocaliva in the current USPI indicated population. Study 405, an adequate and well-controlled study, has demonstrated a statistically and clinically meaningful treatment benefit for event-free and transplant-free survival while supporting the known safety profile of Ocaliva. Multiple RWE analyses provide additional consistent evidence to support that Ocaliva substantially improves transplant and event-free survival. Ocaliva has a well-characterized safety profile based on over 8 years of cumulative global postmarketing experience (>42,000 PYs) and long-term exposure across clinical studies and RWE. The risk for liver injury is low in patients with PBC who are within the Ocaliva USPI indicated population. In addition, the risks that are associated with use of Ocaliva can be adequately and effectively managed. Ocaliva is generally prescribed by specialists (specifically, hepatology and gastroenterology specialists) who are well-versed in Ocaliva and PBC and closely monitor their patients while on therapy.		

CV=cardiovascular; FDA=Food and Drug Administration; FXR=farnesoid X receptor; ITT=intent-to-treat; OCA=obeticholic acid; PBC=primary biliary cholangitis; PPAR=peroxisome proliferator-activated receptor; PY=patient-years; UDCA=ursodeoxycholic acid; US=United States; USPI=United States Prescribing Information

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8. APPENDICES

8.1. Appendix A: Additional Development Details

8.1.1. Comparison of Clinical Studies

A comparison of the key aspects of clinical studies completed subsequent to accelerated approval (i.e., Studies 301 LTSE, 401, and 302) are presented in Table 16.

Table 16: Comparison of Key Aspects of Clinical Studies 301 LTSE, 302, and 401

	Study 301 LTSE	Study 302	Study 401
Study Design and Type of Control	Open-label LTSE durability and safety	DB, placebo control, clinical outcomes	DB, placebo control PK and safety
Population and Eligibility Criteria	Patients with definite or probable PBC diagnosis with an ALP ≥1.67x ULN and/or total bilirubin >ULN to <2x ULN	Patients with definite or probable PBC diagnosis with total bilirubin levels >ULN and ≤5x ULN and/or ALP levels >3x ULN	Patients with definite or probable PBC diagnosis and moderate to severe hepatic impairment (CP-B or CP-C; including MELD scores [6 to 24])
Randomized	193 enrolled into the LTSE and received open-label OCA	A total of 334: Placebo, N=166; OCA N=168	A total of 22: Placebo, N=12; OCA, N=10
Duration	Up to 5 years in LTSE phase	Estimated 10 years with a follow-up time of 6 years. Study was terminated prematurely.	48 weeks Study was terminated prematurely.
Dosing Regimen	Patients receiving placebo started OCA 5 mg QD. Patients already on 5 mg QD continued the same dose. Patients receiving 10 mg QD at the end of the DB phase were titrated down to 5 mg QD. Titration to OCA 10 mg considered, if tolerated.	OCA 5 mg QD or matching placebo. Titration to OCA 10 mg QD at 3 months, if tolerated. Dose and frequency were modified according to the USPI for patients with cirrhosis and classified as CP-B or C.	OCA 5 mg OCA or matching placebo once weekly. Titration to OCA 5 mg twice weekly at Week 12, if tolerated. Titration to OCA 10 mg twice weekly considered every 6 weeks thereafter, if tolerated

	Study 301 LTSE	Study 302	Study 401
Primary Endpoint	Long-term safety Composite endpoint of the percentage of patients with ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease of ≥15% from Baseline.	Original primary endpoint: Time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint: Death (all-cause) Liver transplant MELD score ≥15 Uncontrolled ascites Hospitalization for new onset or recurrence of: • Variceal bleed • Hepatic encephalopathy • SBP Expanded primary endpoint Original endpoint as well as events of portal hypertension syndromes or progression to clinical evidence of portal hypertension without decompensation	PK of OCA Safety

CP-(B or C)=Child-Pugh (B or C); DB=double blind; LTSE=long-term safety extension; MELD=Model for End-Stage Liver Disease; OCA=obeticholic acid; PBC=primary biliary cholangitis; PK=pharmacokinetics; QD=once daily; SBP=spontaneous bacterial peritonitis; USPI=United States Prescribing Information

8.1.2. Comparison of RWE Studies

The RWE package for Ocaliva includes data from multiple data sources, including US healthcare claims database (Komodo Healthcare Map™), data from patient registries including EC arms (Global PBC, UK-PBC, RECAPITULATE), and clinical trials (Table 17). It employs designs that include observational trial emulation, registry analyses, and randomized control trials that are compared to ECs. Collectively, these data provide consistent evidence of clinically meaningful OCA benefit and are independent of data source, healthcare system, geography, or specific study design. With the exception of Study 302 EC, which included patients with advanced disease, patients enrolled in all other studies were generally consistent with patients being treated in current clinical practice. Across all supportive studies, patients were eligible for second-line therapy as they had inadequate response, or were intolerant to, UDCA. The endpoints of transplant-free survival composed of liver transplant and death and event-free survival adding hepatic decompensation were evaluated across studies.

Table 17: Real-world Evidence Studies

	Intercept-Conducted			Independent
	405 RWE[a]	**301 LTSE EC[b]**	**302 EC[c]**	**RECAPITULATE[d]**
Design	OCA-treated group from Komodo Health Claims database OCA eligible but non-OCA-treated group from Komodo Health Claims database	OCA-treated group from 301 LTSE OCA eligible but non-OCA-treated EC group from Global PBC and UK PBC registries	OCA-treated group from 302 OCA-eligible but non-OCA-treated EC group from Komodo Health Claims database	OCA-treated group from Italian PBC Registry OCA-eligible but non-OCA-treated group from Global PBC registry

EC=external control; LTSE=long-term safety extension; OCA=obeticholic acid; PBC=primary biliary cholangitis; RWE=real-world evidence; UK=United Kingdom

[a] Brookhart 2022
[b] Murillo Perez 2022
[c] Kowdley 2022
[d] Terracciani 2024; Vespasiani-Gentilucci 2023

Table 18: Key Elements of Observational Data from External Databases – 301 LTSE EC, 302 EC, RECAPITULATE

	301 LTSE EC	302 EC	RECAPITULATE
Lead Investigator	Global-PBC Study Team	Intercept Pharmaceuticals	RECAPITULATE Study Team Global PBC Study Team
Data Sources (Patients Captured)			
OCA-treated:	301 LTSE (N=209)	302 (N=168)	Italian Registry (N=437)
Non-OCA-treated:	Global PBC Registry (N=1381) UK-PBC Registry (N=2135)	Komodo US Claims Database (N=1051)	Global PBC Registry (N=831)
Time Period Captured	Global PBC: 2012 - 2016 UK-PBC: 2008 - 2020	Komodo: 2014 - 2021	Italian: Initiated 2016 Global PBC: 2000 – 2022
Comparability of OCA-Treated and Non-OCA-Treated	Step 1: Meet Study 301 eligibility criteria Step 2: Propensity score generated IPT weights (both treated and controls weighted)	Step 1: Meet Study 302 eligibility criteria Step 2: Use of SMR weights derived from propensity scores to balance groups (controls are weighted)	Step 1: ALP ≥1.5 ULN and/or 1< total bilirubin <2 mg/dL Non cirrhotic or CP-A cirrhosis or no previous decompensation Step 2: Use of SMR weights derived from propensity scores to balance groups (controls are weighted)
Study Population	Compensated (includes patients without cirrhosis and patients with compensated cirrhosis)	Compensated (includes patients without cirrhosis and patients with compensated cirrhosis) and decompensated patients at index	Compensated (includes patients without cirrhosis and patients with compensated cirrhosis)

	301 LTSE EC	302 EC	RECAPITULATE
Endpoints	Global PBC: Event-free survival Transplant-free survival UK-PBC[a]: Transplant-free survival	Event-free survival[b] Transplant-free survival[b]	Event-free survival Transplant-free survival

CP=Child-Pugh; EC=external control; IPT=inverse probability treatment; LTSE=long-term safety extension; MELD=Model End-Stage Liver Disease; OCA=obeticholic acid; PBC=primary biliary cholangitis; SMR=standardized mortality/morbidity ratio; UK=United Kingdom; US=United States

[a] The UK-PBC registry had protocol violations that: 1) Excluded patients with hepatic decompensation at index; and 2) Did not adequately capture decompensation endpoint events after index.

[b] Given the nature of the Komodo claims database, not all of the endpoints in Study 302 could have been reasonably and reliably assessed. For example, MELD scores and transient elastography values (used to assess for portal hypertension without decompensation) were not available in Komodo.

8.2. Appendix B: Additional Efficacy Details

8.2.1. Study 301/301 LTSE

Study 301 was the Phase 3, 12-month, DB, placebo-controlled study to support accelerated approval based on establishing a reduction in serum ALP. Following the 12-month DB, placebo-controlled period of Study 301, all patients, including those who received placebo, were eligible to participate in an open-label LTSE and were followed for up to an additional 5 years.

A total of 217 patients were enrolled into the 12-month DB phase of the study; of the 198 patients who completed the DB phase, 193 patients (97.5%) enrolled into the LTSE phase. Overall, there was good retention in the LTSE phase of the study: 146 (76%) patients completed the protocol as specified following administrative termination/closure of the study, and 47 (24%) patients discontinued the LTSE prematurely. Most patients discontinued due to study closure by Intercept.

Patient treatment allocation in the DB phase was not made available until the entire study was unblinded. Accordingly, all patients starting in the LTSE phase were initially started on the 5 mg dose, i.e., patients who received placebo started OCA 5 mg, those already on 5 mg continued the same dose, and those who were receiving OCA 10 mg at the end of the DB phase were titrated down to OCA 5 mg. Using this approach, blinding of the entire study was maintained.

All patients continued OCA 5 mg for a minimum of 3 months. After the LTSE Month 3 Visit, OCA dose could be titrated (incrementally from 5 mg to 10 mg to 15 mg, up to 25 mg OCA at a frequency of no more than 1 up titration every 3 months). However, effective with the approved label in 2018, the protocol was amended to align with marketing doses (i.e., OCA 5 mg or 10 mg once daily). Any patient receiving a dose higher than OCA 10 mg was down titrated to ≤10 mg daily.

To account for flexibility of dose adjustments and titration, data are presented by weighted average daily dose (WADD). Of the 193 patients who enrolled into the LTSE phase, 151 (78%) received a WADD of ≤10 mg.

8.2.1.1. Primary Endpoint

The DB phase primary efficacy composite endpoint was the percentage of subjects with ALP <1.67x ULN and total bilirubin ≤ULN and an ALP decrease of ≥15% from baseline at Month 12. For subjects previously randomized to OCA and who continued treatment with OCA in the LTSE and had a WADD ≤10 mg (N=151), the percentage of subjects achieving the primary composite endpoint at the end of the DB phase, i.e., Month 12 (51% for 5-10 mg OCA and 56% for 10 mg OCA), was sustained over the subsequent open-label period. For subjects who received placebo during the DB phase and entered the LTSE, similar increases in responders from the DB baseline were observed at LTSE Month 3 that paralleled those of OCA during the DB placebo phase. Namely, a robust response was observed from LTSE baseline (9%) to LTSE Month 3 (34%), which was increased over the subsequent months of the LTSE treatment phase. Importantly, a response rate of approximately 50% was maintained through LTSE Month 60, irrespective of dose or treatment group.

8.2.1.2. Biochemical Marker Improvement in Study 301

Figure 30 and Figure 31 provide liver biochemistry results over time from Study 301 for both the 12-month DB, placebo-controlled period, as well as the LTSE period. To account for flexibility of dose adjustments and titration, data are presented by WADD. Of the 193 patients who enrolled into the LTSE phase, 151 (78%) received a WADD of ≤10 mg.

First 12 Months: Double-Blind Phase

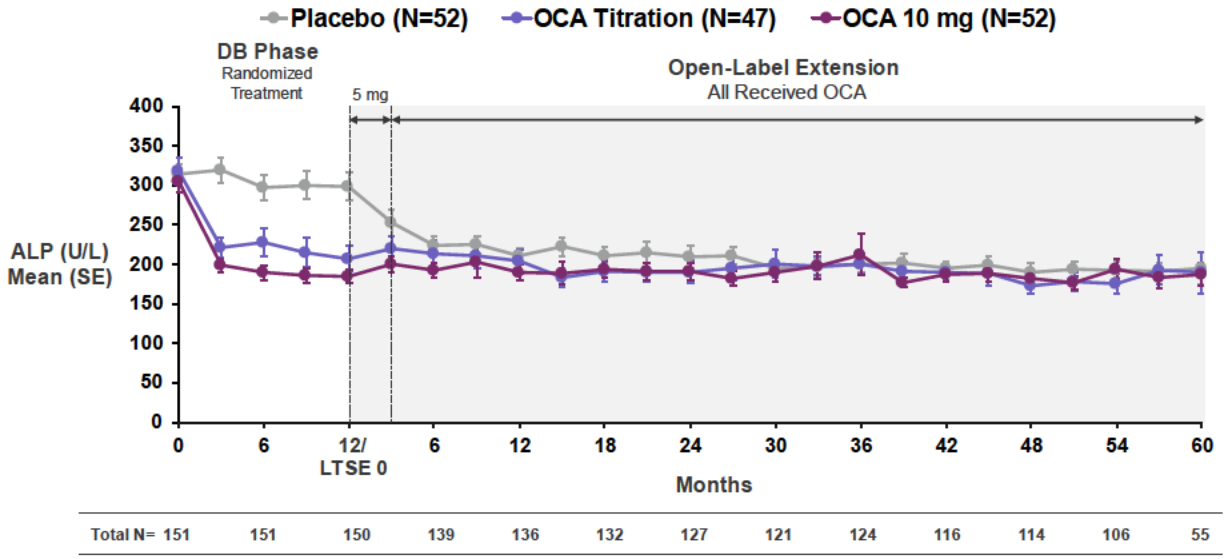
The response to OCA therapy was rapid and robust with clinically meaningful reductions in ALP apparent within 2 weeks of treatment and at every timepoint thereafter, compared to placebo where ALP levels remained highly elevated (Figure 30). A similar response was observed for in other serum markers of cholestasis (GGT) and hepatocellular injury (ALT and AST) (Figure 31).

Up to 60 Months: LTSE Phase

The effect on ALP that was observed for OCA-treated patients in the DB phase was sustained throughout the LTSE phase with long-term treatment for up to 60 months (Figure 30).

Patients who had been randomized to placebo during the DB phase and transitioned to OCA during the LTSE exhibited a nearly identical response to OCA as patients who had been originally randomized to the OCA treatment groups.

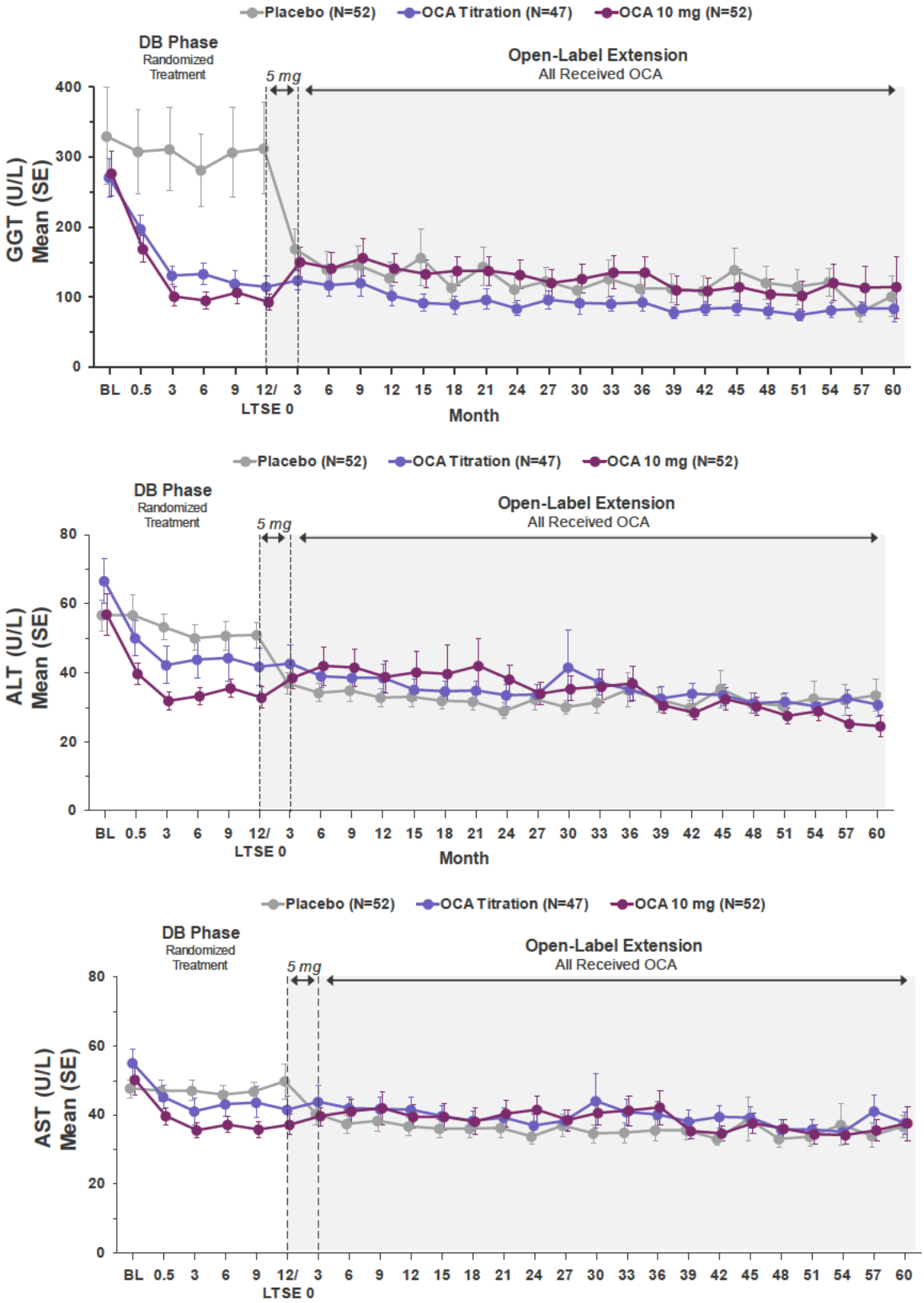
Figure 30: Study 301 LTSE – ALP

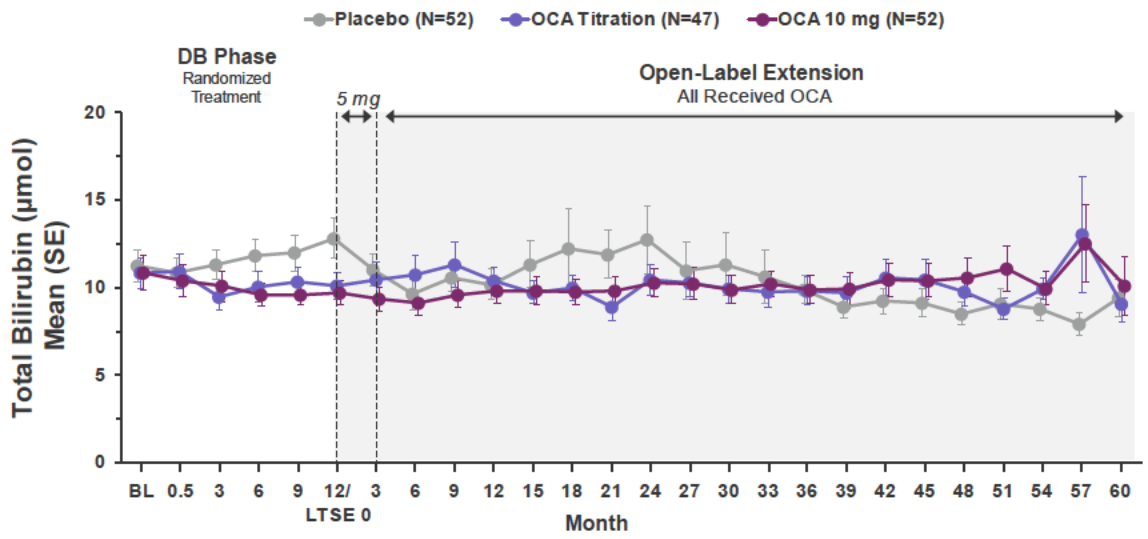


DB=double blind; LTSE=long-term safety extension; OCA=obeticholic acid; WADD=weighted average daily dose
Note: To account for flexibility of dose adjustments and titration, data are presented by WADD. Of the 193 patients who enrolled into the LTSE phase, 151 (78%) received a WADD of ≤10 mg.

Clinically significant reductions were also observed in GGT, ALT, and AST throughout the LTSE period (Figure 31). Total bilirubin levels remained stable and within the normal range throughout the duration of the study. This is consistent with an earlier disease stage population who had normal bilirubin levels at baseline. Importantly, total bilirubin levels that had risen in patients randomized to placebo during the DB phase stabilized within the normal range throughout the LTSE after these patients had initiated OCA (Figure 31).

Figure 31: Study 301 LTSE – GGT, ALT, AST, and Total Bilirubin





DB=double blind; LTSE=long-term safety extension; OCA=obeticholic acid; WADD=weighted average daily dose
Note: To account for flexibility of dose adjustments and titration, data are presented by WADD. Of the 193 patients who enrolled into the LTSE phase, 151 (78%) received a WADD of ≤10 mg.

8.2.2. Study 302

8.2.2.1. Additional Methodology

Study 302 was the largest, randomized, placebo-controlled study conducted in patients with PBC eligible for second-line therapy, and studied a more advanced PBC population than Study 301 in order to capture long-term outcomes of interest. The study was designed to evaluate randomized blinded treatment follow-up for 6 years.

The primary endpoint of Study 302 was to assess the efficacy of OCA compared to placebo using an ITT analysis as measured by time to first occurrence of adjudicated events (i.e., death, liver transplant, Model End-Stage Liver Disease (MELD) ≥15, uncontrolled ascites, or hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis). Key features of the study design included:

- Patients were randomized in a 1:1 ratio to placebo or OCA.
- The 2 treatment groups were compared using a 2-sided log rank test at the 5% level of significance.
- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with an HR of 0.60 to estimate the median survival time used in the sample calculation, and total study duration of 10 years (from first patient enrolled), allowing for 4 years of patient accrual and 6 years of follow up.
- A dropout rate of 10% was assumed.
- Included an EC exploratory analysis in the protocol.

Based on the randomization ratio, significance level, and assumed HR, a total of 127 events (both groups combined) was to provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause

mortality. The background composite hepatic outcomes event rate using data from the Global PBC registry likely underestimated the background rate of decompensation events based on the current understanding of the natural history of PBC.

In addition, based on the remaining assumptions stated above, it was estimated that approximately 428 patients would need to be enrolled to obtain 127 events.

8.2.2.2. Expanded Primary Endpoint Detailed Definition

Table 19: Study 302 - Expanded Primary Endpoint by Group

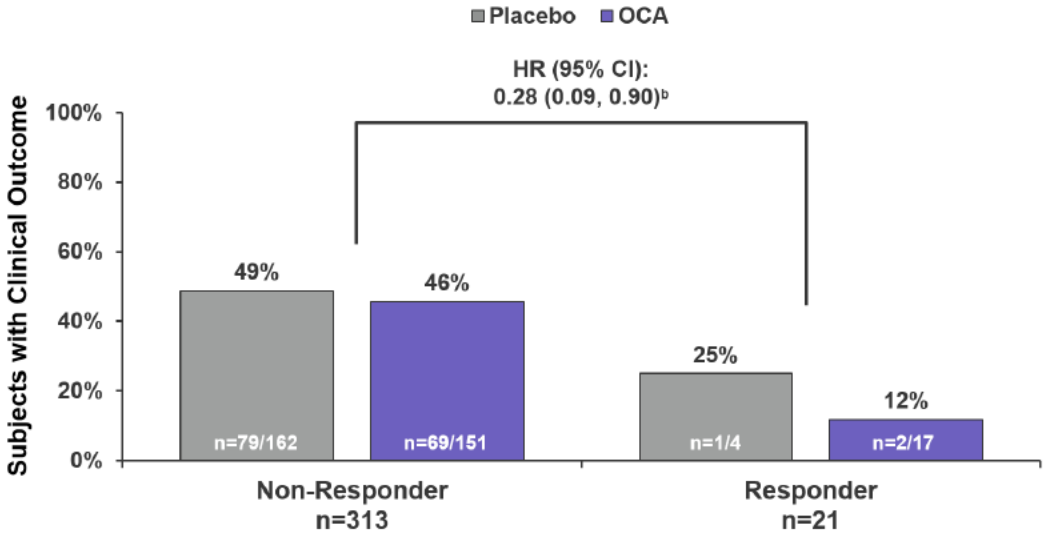
Group 1 (applies to all subjects)
• Death (all-cause) • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis OR presence of >250/mm^3 PMNs in the ascitic fluid), or bacterial empyema (confirmed by diagnostic thoracentesis OR presence of >250/mm^3 PMNs in the pleural fluid) • Uncontrolled or refractory ascites (requiring large volume paracentesis) • Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club [Angeli 2019], portopulmonary syndrome, or hepatopulmonary syndrome) • MELD-Na score ≥15 if MELD-Na <12 at baseline • MELD score ≥15 if MELD-Na ≥12 at baseline
Group 2 (applies to subjects without decompensation at Baseline)
Progression to decompensated liver disease (for subjects without decompensation at baseline), prioritized as follows: • New onset of hepatic hydrothorax, variceal bleeding, or ascites requiring treatment with sodium restriction, diet modification, or diuretics • Hepatic encephalopathy requiring lactulose and/or rifaximin • New onset of Child-Pugh ≥7 or total bilirubin >3 mg/dL
Group 3 (applies to subjects without decompensation or clinical evidence of portal hypertension at Baseline)
Progression to clinical evidence of portal hypertension without decompensation (for subjects without decompensation or clinical evidence of portal hypertension at baseline) • Endoscopic evidence of portal hypertension without bleeding (i.e., gastroesophageal varices [requiring banding or progression to large varices if no or small varices were observed at baseline] or portal hypertensive gastropathy • Platelets <150 x 10^9/L with splenomegaly and/or with transient elastography >15 kPa

MELD=Model for End-Stage Liver Disease; PMN=polymorph leukocyte

8.2.2.3. Association of Biochemical Marker Improvement and Clinical Outcomes

The observed HR (95% CI) of responders to non-responders was 0.28 (0.09, 0.90), with a nominal p-value=0.006, indicating responders to the Study 301 primary endpoint were less likely to experience a negative outcome based on the primary expanded composite endpoint (Figure 32). The magnitude of treatment effect in favor of OCA appeared to be greater (17/168 [10.1%]) compared to placebo (4/166 [2.4%]). These data from Study 302 further support the biochemical response observed in Study 301 for accelerated approval.

Figure 32: Study 302 – Association of Biochemical Marker Improvement and Clinical Outcomes



HR=hazard ratio; ITT=intent to treat, OCA=obeticholic acid

[a] Study 301 primary endpoint: A biochemical responder is defined as a patient who attains an ALP <1.67 times the ULN and total bilirubin ≤ULN and an ALP decrease of ≥15% from Baseline at Month 12 visit. Patients missing values at Month 12 are considered non-responders.

[b] Adjusted for Baseline Covariate. HR was estimated using stratified Cox's proportional hazards model with responder as an independent variable and the treatment group as strata. The results represent the ratio of Responder to Non-responder. A HR <1 indicates an advantage for Responder.

Clinical outcome is the expanded primary endpoint.

8.2.3. Study 405

8.2.3.1. Komodo Database Reflective of PBC

Table 20: PBC Patients Well-represented in Komodo Database

	Komodo Estimate 2021	Lu et al, 2018 (2004-2014) (FOLD Consortium)
N **Total N (PBC)**	330 million (150 million patients w/ closed claims) N=41,426	14.5 million (Health system population) N=3,488
Estimated US **Prevalence, total** **Per 100,000**	105,506 40.9	-- 39.2 (2014 estimate)
Age, Mean (SD))	61.9 (13.2) at time of entry in cohort	59.2 (12.9) at time of diagnosis 63.7 (13.0) at most recent encounter
Sex, n (%)		
Female	34,381 (83.0)	2850 (81.7)
Male	7,045 (17.0)	638 (18.3)
Race/ethnicity, n (%)		
White	21,505 (51.9)	2227 (63.8)
African American	2411 (5.8)	286 (8.2)
Asian	1117 (2.7)	252 (7.2)
Other	1382 (3.3)	--
Unknown	9620 (23.2)	723 (20.7)
Hispanic/Latino[a]	5391 (13.0)	721 (20.7)

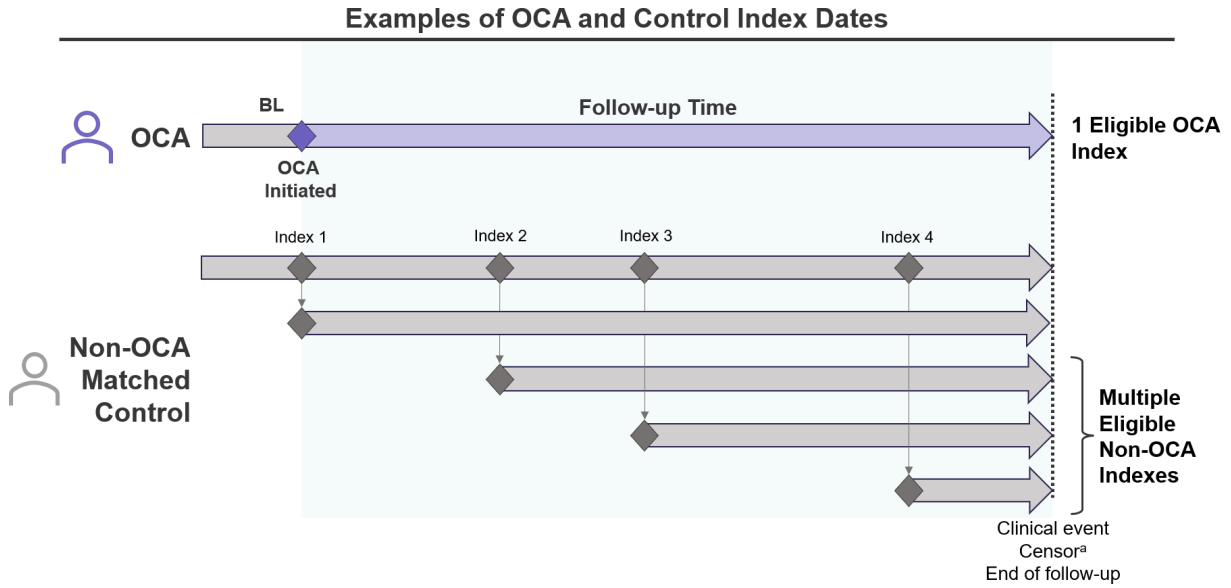
[a] In FOLD, Hispanic/not Hispanic is reported as ethnicity, not as part of race.
Sources: Buchanan-Peart 2023; Lu 2018a, Lu 2018b

8.2.3.2. OCA and Control Index Dates

As shown in Figure 33, the trial emulation design utilized multiple index dates. Each time a patient met the UDCA failure (inadequate response/intolerance/discontinuation) definition or the definition of OCA initiation, in addition to all other eligibility criteria, they contributed an index to the study. The first date of prescription claim for OCA after UDCA failure (inadequate response, intolerance, or discontinuation) was defined as the index date for OCA-treated group. The dates of healthcare utilization resulting in a claim in which there was evidence of UDCA failure during which OCA, or fibrates were not utilized, were used as indices for the non–OCA-treated control group. While OCA-treated patients could contribute multiple control indexes before initiating OCA therapy, they could not contribute additional indices after OCA initiation. Therefore, each patient could contribute, at most, 1 OCA index.

Patients were required to have closed medical claims for 12 months and laboratory data preceding the index (i.e., the pre-index period) to establish medical history of PBC and OCA eligibility, and to generate the propensity scores and standardized morbidity ratio weights. For each index, patients were followed until they logged their first composite endpoint, were censored at treatment change (defined below), were lost to follow-up, or end of study period on 31 Dec 2021, whichever came first.

Figure 33: Study 405 – Trial Emulation Study Design Utilized Multiple Index Dates



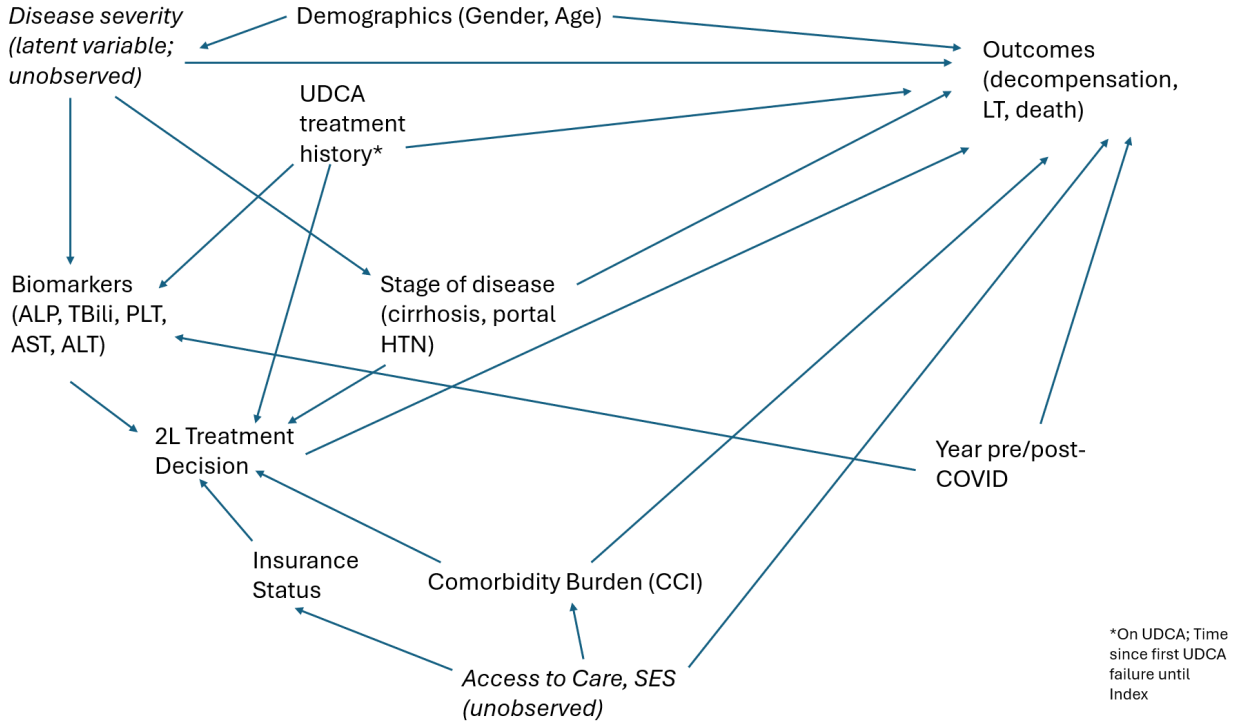
BL=baseline; OCA=obeticholic acid; UDCA=ursodeoxycholic acid

[a] OCA-treated indexes were censored 90 days after OCA discontinuation or if fibrates were initiated. Control indexes were censored if a patient-initiated OCA therapy, fibrate therapy, or reinitiated UDCA for patients who had discontinued UDCA therapy for >6 months, or the end of the study period (31 Dec 2021), whichever came first.

8.2.3.3. Pre-Specified Prognostic Factors and Weighting

In the absence of randomization, a rigorous method was employed to balance treatment arms. Key baseline predictors of outcomes were pre-specified by the independent, expert Medical Team of gastroenterologists and hepatologists. The pre-specified factors included pre/post COVID calendar year, sex, age, labs, clinical evidence of portal hypertension, cirrhosis, CCI - a validated measure encompassing major comorbidities including CV disease and cancers associated with survival, UDCA use, and insurance type. Figure 34 is a depiction of the relationship of these key prognostic factors, which because of their association with other factors, reflect a comprehensive set of known risks, both measured and unmeasured, in the PBC disease pathway. For example, while certain measures of disease severity such as Fibroscan and biopsy were not available in the data source for Study 405, the availability of related key laboratory measures (ALP, total bilirubin, AST, ALT, and platelets) and diagnosis records of cirrhosis and portal hypertension allowed for appropriate characterization of the disease severity in both the OCA-treated and non-OCA-treated cohorts.

Figure 34: Directed Acyclical Graph (DAG) of Key Prognostic Factors in the PBC Disease Pathway



2L=second-line, CCI=Charlson Comorbidity Index, HTN=hypertension, LT=liver transplant, PBC=primary biliary cholangitis; UDCA=ursodeoxycholic acid, SES=socioeconomic status

Propensity score-based weighting adjusted for differences in covariate distribution using SMR weights was employed to balance the cohorts. Prior to weighting, differences between the OCA and non-OCA-treated cohorts were observed for certain variables. ALP was higher for OCA index dates than non-OCA index dates, and the CCI was lower for OCA index dates than non-OCA index dates. These variables demonstrate aspects of clinician decision making for OCA initiation. This indicates that OCA index dates had PBC disease at a higher risk of disease progression and thus was a more conservative estimate compared to non-OCA index dates.

8.2.3.4. Demographic and Baseline Characteristics

Table 21: Study 405 – Demographics and Baseline Characteristics (Unweighted and Weighted)

Mean (SD) [unless otherwise noted]	Unweighted		Weighted	
	Non OCA-treated N=11246	OCA-treated N=403	Non OCA-treated N=405.37	OCA-treated N=403
Sex (Female), n (%)	10146.0 (90.2)	369.0 (91.6)	369.5 (91.1)	369.0 (91.6)
Age (years)	61.1 (11.7)	56.2 (10.6)	55.9 (12.6)	56.2 (10.6)
ALP (U/L)	198.9 (104.1)	292.1 (154.4)	294.2 (152.7)	292.1 (154.2)
Total bilirubin (mg/dL)	0.66 (0.41)	0.70 (0.46)	0.70 (0.45)	0.70 (0.46)
ALT (U/L)	34.9 (28.2)	51.5 (41.2)	52.7 (45.6)	51.5 (41.2)
AST (U/L)	35.8 (23.4)	48.8 (34.1)	49.6 (36.5)	48.8 (34.0)
ALB (g/dL)	4.1 (0.4)	4.1 (0.3)	4.1 (0.4)	4.1 (0.3)
Clinical evidence of portal hypertension (Yes), n (%)	2887.0 (25.7)	95.0 (23.6)	95.0 (23.4)	95.0 (23.6)
Cirrhosis (Yes), n (%)	4936.0 (43.9)	203.0 (50.4)	204.6 (50.5)	203.0 (50.4)
CCI Score	3.7 (2.7)	3.0 (2.3)	3.0 (2.3)	3.0 (2.3)
On UDCA (Yes), n (%)	7236.0 (64.3)	292.0 (72.5)	294.6 (72.7)	292.0 (72.5)
Time (months) Since First UDCA Failure until the index	7.3 (13.6)	1.1 (3.8)	1.2 (3.2)	1.1 (3.8)
Region				
Northeast	2490 (22.1)	82 (20.3)	84.3 (20.8)	82 (20.3)
Midwest	1075 (9.6)	38 (9.4)	38.3 (9.4)	38 (9.4)
West	2735 (24.3)	97 (24.1)	105.90 (26.1)	97 (24.1)
South	4893 (43.5)	186 (46.2)	175.35 (43.3)	186 (46.2)
Territory	13 (0.1)	0	0.40 (0.1)	0
Insurance Type				
Commercial	5015 (44.6)	194 (48.1)	195.5 (48.2)	194 (48.1)
Self-insured/Exchanges	1803 (16.0)	68.0 (16.9)	67.4 (16.6)	68.0 (16.9)
Medicare	2763 (24.6)	60.0 (14.9)	58.2 (14.4)	60.0 (14.9)
Medicaid	1524 (13.6)	73 (18.1)	75.9 (18.7)	73 (18.1)
Dual eligible	94 (0.8)	6 (1.5)	6.1 (1.5)	6 (1.5)
Other	47 (0.4)	2 (0.5)	2.2 (0.6)	2 (0.5)

ALB=albumin; CCI=Charlson Comorbidity Index; OCA=obeticholic acid; UDCA= ursodeoxycholic acid

8.2.3.5. Quantitative Bias Analysis

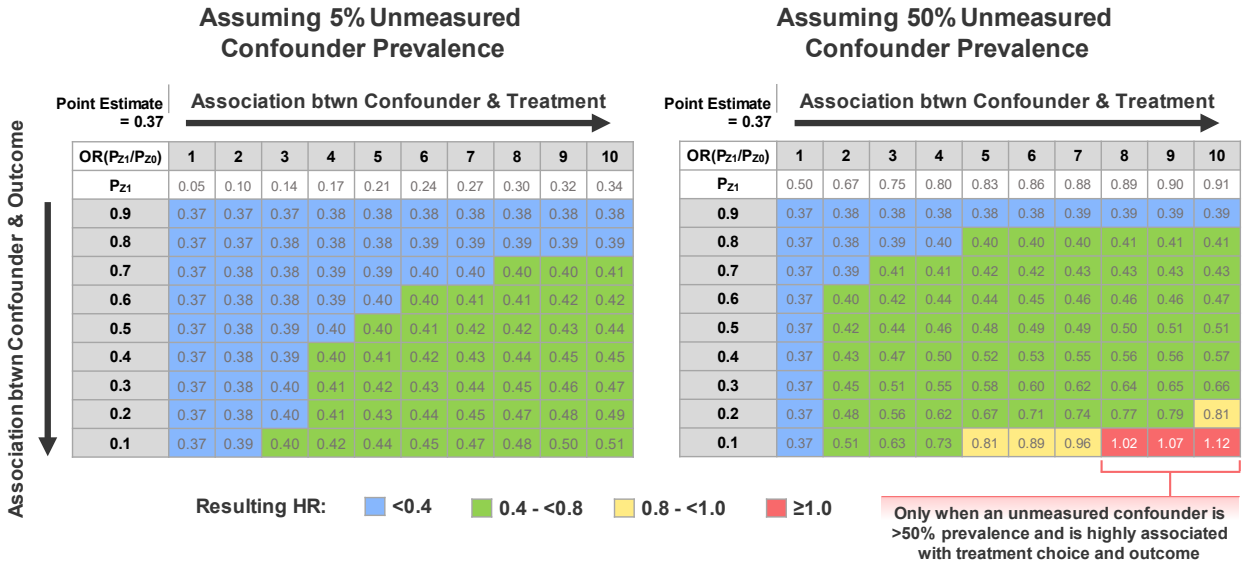
Due to the nature of RWD, the possibility of residual unmeasured confounding may have impacted the results of Study 405. To account for this, a quantitative bias analysis was performed to assess sensitivity of the estimates on the primary endpoint.

Analyses were conducted using the observed HR of 0.37 with confounder prevalence set at 5% (low prevalence confounder) and at 50% (high prevalence confounder), and an odds ratio of association varying between 1 (representing no association) to 10 (representing a high association between confounder and treatment). Of note a strong confounder present in 50% of the population was unlikely given the Medical Team's ascertainment of important prognostic factors depicted in Figure 34, such as ALP, total bilirubin, and the presence of cirrhosis. It is possible that a variable not reflected in database such as Fibroscan® or biopsy could have provided additional information in the captured variables. However, there is correlation between Fibroscan® and biopsy with the captured variables. The potential impact of information outside of variables captured in the database potentially leading to residual and unmeasured confounding was then addressed by the quantitative bias analysis exercise.

The heat maps shown in Figure 35 demonstrate the degree of unmeasured confounding that would need to be present to move the HR from its current value of <0.4 depicted in blue to values that no longer support a benefit from OCA (HR >1.0) depicted in red. Only an unmeasured confounder that is both strongly associated with exposure and outcome, and is highly prevalent in the population, would have the potential to shift the HR towards the null, as shown in Figure 35. Given the thorough understanding of the etiology and risks associated with disease progression in PBC identified by the independent expert Medical Team, such a strongly associated and highly prevalent confounder, which is wholly unrelated to the measured key prognostic factors outlined in the DAG (Figure 34), is not expected.

Therefore, the quantitative bias analysis demonstrates that the observed benefit is robust even in the face of unmeasured confounding.

Figure 35: Study 405 – Quantitative Bias Analysis for the SMR-weighted Composite Endpoint Hazard Ratio



OR(P_{Z1}/P_{Z0})	1	2	3	4	5	6	7	8	9	10
P_{Z1}	0.05	0.10	0.14	0.17	0.21	0.24	0.27	0.30	0.32	0.34
0.9	0.37	0.37	0.37	0.38	0.38	0.38	0.38	0.38	0.38	0.38
0.8	0.37	0.37	0.38	0.38	0.38	0.39	0.39	0.39	0.39	0.39
0.7	0.37	0.38	0.38	0.39	0.39	0.40	0.40	0.40	0.40	0.41
0.6	0.37	0.38	0.38	0.39	0.40	0.40	0.41	0.41	0.42	0.42
0.5	0.37	0.38	0.39	0.40	0.40	0.41	0.42	0.42	0.43	0.44
0.4	0.37	0.38	0.39	0.40	0.41	0.42	0.43	0.44	0.45	0.45
0.3	0.37	0.38	0.40	0.41	0.42	0.43	0.44	0.45	0.46	0.47
0.2	0.37	0.38	0.40	0.41	0.43	0.44	0.45	0.47	0.48	0.49
0.1	0.37	0.39	0.40	0.42	0.44	0.45	0.47	0.48	0.50	0.51

OR(P_{Z1}/P_{Z0})	1	2	3	4	5	6	7	8	9	10
P_{Z1}	0.50	0.67	0.75	0.80	0.83	0.86	0.88	0.89	0.90	0.91
0.9	0.37	0.38	0.38	0.38	0.38	0.38	0.39	0.39	0.39	0.39
0.8	0.37	0.38	0.39	0.40	0.40	0.40	0.40	0.41	0.41	0.41
0.7	0.37	0.39	0.41	0.41	0.42	0.42	0.43	0.43	0.43	0.43
0.6	0.37	0.40	0.42	0.44	0.44	0.45	0.46	0.46	0.46	0.47
0.5	0.37	0.42	0.44	0.46	0.48	0.49	0.49	0.50	0.51	0.51
0.4	0.37	0.43	0.47	0.50	0.52	0.53	0.55	0.56	0.56	0.57
0.3	0.37	0.45	0.51	0.55	0.58	0.60	0.62	0.64	0.65	0.66
0.2	0.37	0.48	0.56	0.62	0.67	0.71	0.74	0.77	0.79	0.81
0.1	0.37	0.51	0.63	0.73	0.81	0.89	0.96	1.02	1.07	1.12

HR=hazard ratio; OR=odds ratio for the association between the unmeasured confounder and the outcome; P_{Z0}=prevalence of the confounder among the OCA-treated; P_{Z1}=calculated prevalence of the confounder among the non-OCA-treated; SMR=standardized mortality/morbidity ratio

8.2.3.6. Other Sensitivity Analysis

The primary efficacy endpoint analysis followed an as-treated (on treatment) approach, which is conventionally used in observational studies to evaluate the association between exposure/treatment and outcomes for patients in the real world on chronic therapy (RCT-DUPLICATE, Wang 2023).

A sensitivity analysis on the 405 primary endpoint was conducted using a similar approach to Study 302 (i.e., ITT approach which counted outcomes even after patients stopped study visits or cross over to commercial therapy). This analysis evaluated 2 ITT approaches, which allowed for treatment crossover between groups:

- OCA indexes not censored after discontinuation (ITT approach 1)
- OCA indexes not censored after discontinuation and control indexes (ITT approach 2):
  - Not censored at OCA initiation
  - Not censored at UDCA reinitiation (only for control indexes in which UDCA failure was defined by discontinuation)

Acknowledging the inherent limitations of ITT analyses for a real-world analysis of a chronic therapy, the resulting HRs were generally consistent with the primary analysis (Figure 36).

Figure 36: Study 405 – Further Sensitivity Analyses Show Robustness of Real-world Benefit

Time to Death, Liver Transplant or Hospitalization for Hepatic Decompensation

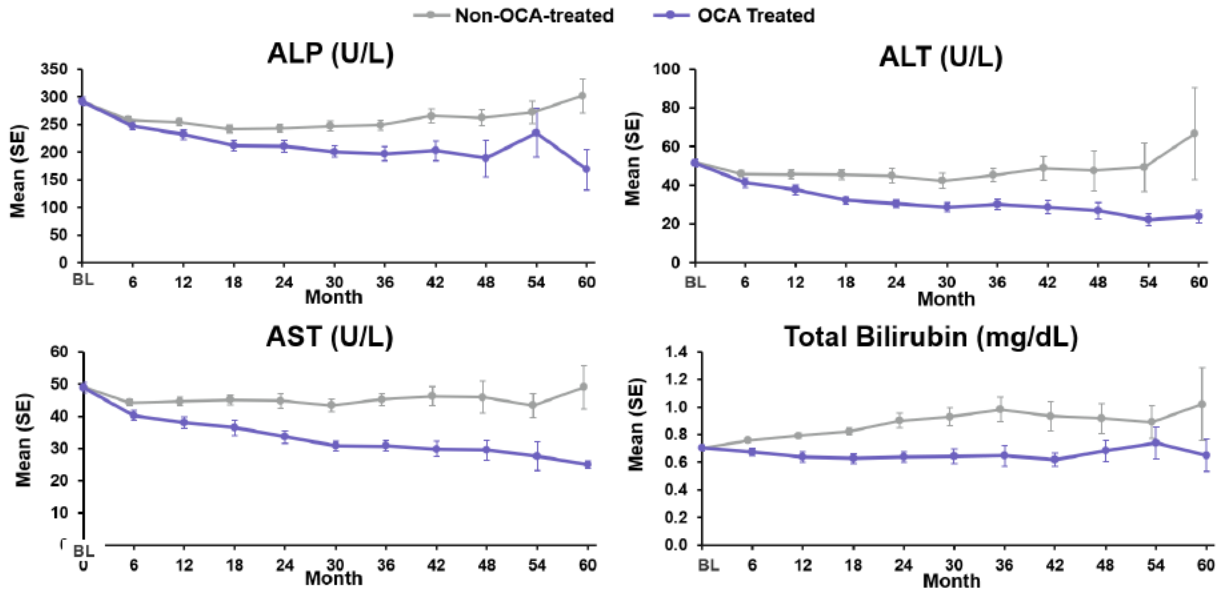
Endpoint	Hazard Ratio (95% CI)
Primary Endpoint (As-Treated)	0.37 (0.14, 0.75)
Sensitivity Analyses	
ITT 1: OCA Indexes not Censored after Discontinuation	0.59 (0.34, 1.00)
ITT 2: OCA Indexes not Censored after Discontinuation and Control Indexes not Censored at OCA Initiation or Not Censored at UDCA Reinitiation	0.64 (0.38, 1.05)

OCA=obeticholic acid; UDCA=ursodeoxycholic acid

8.2.3.7. Biochemical Marker Improvement in Study 405

Study 405 demonstrated a benefit of OCA on key biochemical markers of disease progression. While markers were balanced between OCA and control groups at the index visit, over time the group receiving OCA maintained bilirubin and improved ALP, ALT, and AST, while the control group remained unchanged or worsened (Figure 37).

Figure 37: Study 405 – ALP, ALT, AST, and Total Bilirubin



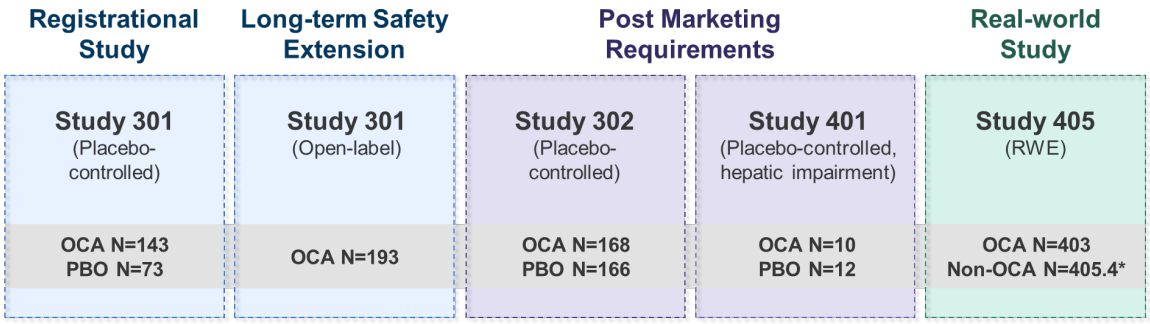
OCA=obeticholic acid
Note: GGT was not comprehensively collected in Study 405.

8.3. Appendix C: Additional Safety Details

8.3.1. Source of Data for Safety

The clinical studies contributing to the safety assessment are as shown in Figure 38.

Figure 38: Clinical Studies Contributing to PBC Safety Assessment



OCA=obeticholic acid; PBC=primary biliary cholangitis; PBO=placebo; RWE=real-world evidence; SMR=standardized mortality/morbidity ratio
* Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group
Note: Once patients with moderate or severe hepatic impairment became contraindicated after the 2021 USPI label update, Intercept terminated Study 401 with 44% (22/50) of anticipated enrollment. Study 401 data are summarized in Appendix D, Section 8.4.

8.3.2. Extent of Exposure

Total exposure to OCA in person-years for Studies 301 DB, 301 LTSE, 302, and 405 is presented in Table 22.

Table 22: Total OCA Exposure

	301 Double-blind		301 LTSE	302	405
	OCA 5 to 10 mg N=70	OCA 10 mg N=73	OCA N=193	OCA N=168	OCA N=403
Total Exposure (Person-Years)	65.5	61.7	922.1	403.1	562.6

LTSE=long-term safety extension; OCA=obeticholic acid
Note: Total exposure in person-years is calculated as (mean number of days OCA per treatment group x N) / 365.25

8.3.3. Overview of Safety from Registrational Phase 3 Study DB 301 and 301 LTSE

Data from Study 301 established the safety profile of Ocaliva. All patients had earlier-stage disease, and the majority of the patients from the LTSE met the criteria for the current USPI (i.e., did not have clinical evidence of portal hypertension or hepatic decompensation).

An overview of safety, including data from the DB and 5-year LTSE is presented in Table 23.

Double-Blind Phase of Study 301 (12-Month)

During the 12-month, DB period of Study 301, no clinically meaningful differences were observed between the OCA and placebo groups for overall TEAEs, and administration of OCA 5 mg and OCA 10 mg was generally well tolerated. The majority of TEAEs reported in the OCA groups were due to pruritus.

While more OCA-treated patients reported an SAE, there was no dose-response pattern, and none of the serious TEAEs were considered related to investigational product by the Investigator. The incidence of individual SAEs by preferred term was low and occurred in 1 patient each except for osteoarthritis and varicose veins, which occurred in 2 OCA-treated patients each, and upper gastrointestinal hemorrhage, which occurred in 1 OCA-treated patient and 1 placebo-treated patient. No hepatobiliary SAEs were reported, and one cardiac SAE occurred in each of the placebo and OCA titration groups.

There was a single death recorded in the OCA group due to cardiac failure, which occurred in an 81-year-old patient with a past medical history of congestive heart failure and was considered unlikely related to treatment. No events led to liver transplantation over the 12-month DB study duration.

Long-term Safety Extension Phase of Study 301 (Up to 5 Years)

During the 301 LTSE period, there was minimal change over 5 years in the proportion of patients reporting TEAEs. Overall, 151 (78%) patients reported pruritus (per the standardized MedDRA queries definition for AEs of special interest); of these patients, 14 (7%) discontinued due to pruritus throughout the study.

Overall, 61 (32%) subjects experienced a serious TEAE. There was no apparent pattern to the types of serious TEAEs. No patient had a serious TEAE of pruritus. The majority of serious TEAEs were considered not or unlikely related to OCA. Two (1%) subjects had a TEAE that led to death (the deaths were deemed by the Investigator as not related to OCA). One patient died approximately 6 months after the start of the LTSE phase due to multi-organ failure resulting from sepsis secondary to bacterial endocarditis. The event of sepsis was considered by the Investigator as not related to OCA. A second patient died approximately 5 years after the start of the LTSE phase due to complications secondary to severe alcohol-associated hepatitis; the event was considered not related to OCA by the Investigator.

Three patients underwent orthotopic liver transplantation during the LTSE phase of 747-301. Two of the patients received placebo in the DB phase. At LTSE baseline all 3 patients had progressed to cirrhosis with evidence of portal hypertension (contraindication per the current USPI). One patient was transplanted for recurrent multifocal hepatocellular carcinoma (3 years and 8 months after enrolling into the LTSE) and the other 2 patients had gradual declines in synthetic liver function with recurrent episodes of decompensation events (1 patient had a liver transplant 1 year after enrolling into the LTSE and the other patient had a liver transplant 2 years and 2 months after enrolling to the LTSE). All patients discontinued from the study after undergoing liver transplantation and no additional follow-up was reported.

Table 23: Overview of Safety in Study 301 (Safety Population)

n (%)	Double-blind (12 months)			LTSE (up to 5 years)
	Placebo N=73	OCA 5→10 mg N=70	OCA 10 mg N=73	Total OCA N=193
Any TEAEs	66 (90)	65 (93)	69 (95)	189 (98)
Any SAEs	3 (4)	11 (16)	8 (11)	61 (32)
TEAEs Leading to Death	0	1 (1)	0	2 (1)
TEAEs Leading to Study Discontinuation	2 (3)	5 (7)	8 (11)	26 (13)
Study Discontinuation due to Pruritus[a]	0	1 (1)	7 (10)	14 (7)
Liver Transplants	0	0	0	3 (2)

LTSE=long-term safety extension; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

[a] Based on preferred term.

Note: Safety data included all patients who received at least 1 dose of investigational product in Study 301, and any data after 30 days of investigational product discontinuation are excluded.

8.3.4. Overview of Safety from Study 302

An overview of safety from Study 302 is presented in Table 24.

Treatment with OCA was generally well-tolerated in patients with PBC, and the overall safety profile was consistent with that observed in the registrational Study 301. The incidence of TEAEs and SAEs was similar across treatment groups. The most common TEAE reported in the OCA group was pruritus. The incidence of TEAEs leading to discontinuation of investigational product was higher in the OCA group than the placebo group, which was driven by TEAE of pruritus. However, most of the pruritus TEAEs were mild to moderate in severity.

A total of 7 subjects had a TEAE leading to death (5 in OCA-treated subjects: acute respiratory failure, respiratory failure, subarachnoid hemorrhage, sepsis, and lower respiratory tract infection; and 2 in placebo-treated subjects: sarcopenia and hepatocellular carcinoma). All TEAEs leading to death were considered not related or unlikely related to the investigational product. The proportion of patients undergoing liver transplantation was similar between the treatment groups with 20 (11.9%) patients in the OCA group and 18 (10.8%) patients in the placebo group.

Table 24: Overview of Safety in Study 302 (Safety Population)

n (%)	Placebo N=166	OCA N=168
Any TEAEs	158 (95.2)	162 (96.4)
Any SAEs	53 (31.9)	53 (31.5)
TEAEs Leading to Death	2 (1.2)	5 (3.0)
TEAEs Leading to Study Discontinuation	19 (11.4)	29 (17.3)
Investigational Product Discontinuation due to Pruritus	3 (1.8)	19 (11.3)
Liver Transplants	18 (10.8)	20 (11.9)

OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event
Note: With the exception of liver transplants, which is inclusive of events occurring on-study, safety data included all patients who received at least 1 dose of investigational product in Study 302, and any data after 30 days of investigational product discontinuation are excluded.

8.3.5. Safety Topics of Interest from Studies with a Control Group (301, 302 and 405)

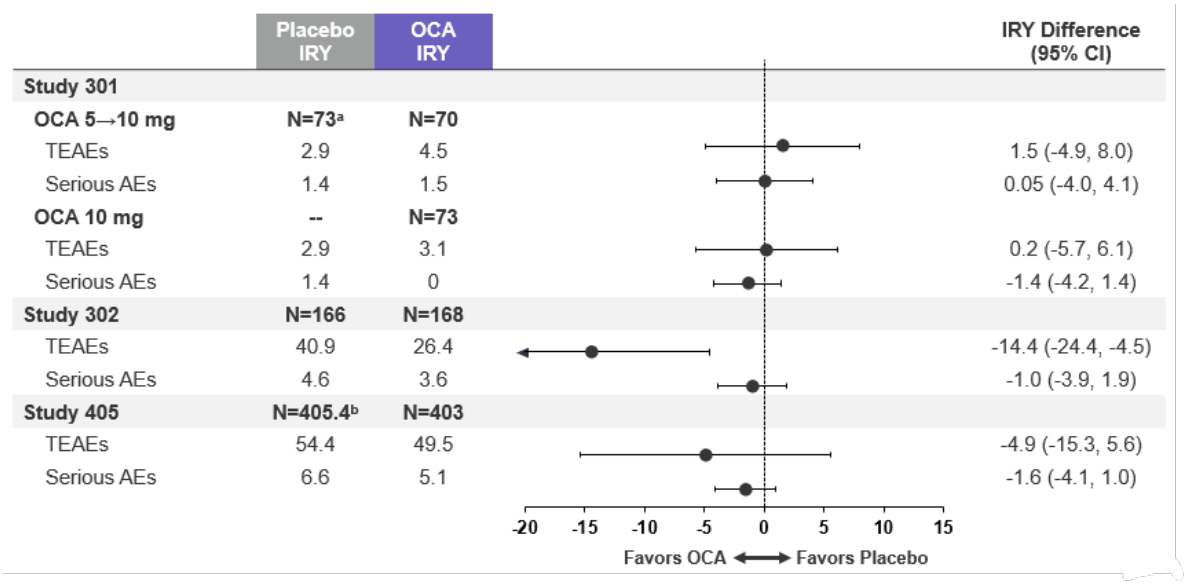
To account for the differences in total exposure across studies as shown in Table 22 and further minimize the bias observed in the ITT population of Study 302, treatment-emergent EAIRs for these safety topics are presented below.

8.3.5.1. Hepatic

8.3.5.1.1. Exposure-adjusted Incidence Rates Hepatic Adverse Events Across Studies

There was no excess risk for hepatic AEs in OCA-treated patients with PBC compared to placebo (Table 25). The incidence of exposure-adjusted hepatic events was lower in the OCA group compared to the placebo group across Study 302 and Study 405. In Study 301, the exposure-adjusted risk difference for serious hepatic AEs was near zero with CIs including zero in the OCA titration (5mg →10 mg) group and OCA 10 mg groups, respectively.

Table 25: Investigator-reported Hepatic Adverse Events per 100 Patient Years in Studies 301, 302 and 405 (Safety Population)



AE=adverse event; IRY=number of patients with event per 100 patient years; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; TEAE=treatment-emergent adverse event

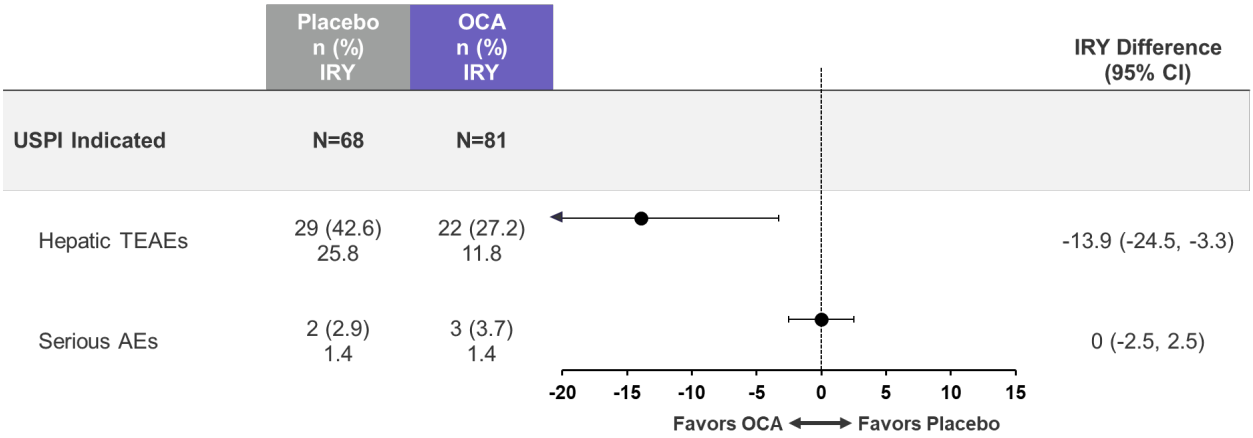
[a] One placebo group evaluated in Study 301.

[b] Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group; serious AEs were defined as events that led to death and/or hospitalization.

USPI Indicated Population

The incidence of hepatic TEAEs and SAEs in the USPI indicated population of Study 302, which was based on baseline disease status, are summarized in Table 26. The incidence of hepatic TEAEs in the OCA group (27.2%) was lower than in the placebo group (42.6%) in the USPI indicated population. The difference observed between the OCA and placebo groups is more pronounced when considering the incidence of exposure-adjusted hepatic TEAEs (11.8 per 100 PYs in the OCA group and 25.8 per 100 PYs in the placebo group). No difference was observed between treatment groups in exposure-adjusted hepatic SAEs (1.4 per 100 PYs in the OCA group and 1.4 per 100 PYs in the placebo group).

Table 26: Investigator-reported Hepatic Adverse Events per 100 Patient Years in USPI Indicated Population from Study 302 (Safety Population)



AE=adverse event; IRY=number of patients with event per 100 patient years; OCA=obeticholic acid; PH=portal hypertension; TEAE=treatment-emergent adverse event; USPI=United States Prescribing Information

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

8.3.5.1.2. eDISH in Study 302

In Study 302, eDISH screening plot analyses were utilized to evaluate potential drug-induced serious hepatotoxicity based on central and local laboratory results. eDISH plots were created at baseline and at peak lab excursion (peak ALT and total bilirubin values; peak values may have occurred at different timepoints over the observation period).

- **Biochemical Hy's Law Range:** >3x ULN for ALT and >2x ULN for total bilirubin.
- **Temple's Corollary Range:** >3x ULN for ALT, ≤2x ULN for total bilirubin.
- **Cholestasis Range:** >2x ULN for total bilirubin, ≤3x ULN for ALT.
- **Near normal range:** ≤2x ULN for total bilirubin; ≤3x ULN for ALT; and >ULN for ALT and total bilirubin
- **Normal range:** ≤ULN for ALT and total bilirubin.

A table with eDISH shifts from baseline quadrant to peak quadrant in the overall safety population, USPI indicated population, and USPI contraindicated population is presented in Table 27.

Table 27: Study 302 – Shift of eDISH Quadrants from Baseline to Peak Excursion (Safety Population)

n (%)	Overall		USPI Indicated		USPI Contraindicated	
	Placebo N=166	OCA N=168	Placebo N=68	OCA N=81	Placebo N=98	OCA N=87
Baseline: Normal						
Normal Range	0	2 (1.2)	0	1 (1.2)	0	1 (1.1)
Near Normal Range	3 (1.8)	3 (1.8)	3 (4.4)	1 (1.2)	0	2 (2.3)
Temple's Corollary Range	0	0	0	0	0	0
Cholestasis Range	1 (0.6)	0	0	0	1 (1.0)	0
Biochemical Hy's Law Range	**0**	**0**	**0**	**0**	**0**	**0**
Baseline: Near Normal						
Normal Range	1 (0.6)	1 (0.6)	0	1 (1.2)	1 (1.0)	0
Near Normal Range	49 (29.5)	66 (39.3)	25 (36.8)	40 (49.4)	24 (24.5)	26 (29.9)
Temple's Corollary Range	15 (9.0)	10 (6.0)	11 (16.2)	9 (11.1)	4 (4.1)	1 (1.1)
Cholestasis Range	25 (15.1)	23 (13.7)	2 (2.9)	1 (1.2)	23 (23.5)	22 (25.3)
Biochemical Hy's Law Range	**9 (5.4)**	**4 (2.4)**	**3 (4.4)**	**1 (1.2)**	**6 (6.1)**	**3 (3.4)**
Baseline: Cholestasis						
Normal Range	0	0	0	0	0	0
Near Normal	0	0	0	0	0	0
Temple's Corollary Range	0	1 (0.6)	0	0	0	1 (1.1)
Cholestasis Range	15 (9.0)	10 (6.0)	0	2 (2.5)	15 (15.3)	8 (9.2)
Biochemical Hy's Law Range	**2 (1.2)**	**4 (2.4)**	**1 (1.5)**	**0**	**1 (1.0)**	**4 (4.6)**

n (%)	Overall		USPI Indicated		USPI Contraindicated	
	Placebo N=166	**OCA N=168**	**Placebo N=68**	**OCA N=81**	**Placebo N=98**	**OCA N=87**
Baseline: Temple's Corollary						
Normal Range	0	0	0	0	0	0
Near Normal	6 (3.6)	10 (6.0)	3 (4.4)	6 (7.4)	3 (3.1)	4 (4.6)
Temple's Corollary Range	13 (7.8)	13 (7.7)	11 (16.2)	9 (11.1)	2 (2.0)	4 (4.6)
Cholestasis Range	1 (0.6)	1 (0.6)	1 (1.5)	0	0	1 (1.1)
Biochemical Hy's Law Range	**15 (9.0)**	**11 (6.5)**	**6 (8.8)**	**8 (9.9)**	**9 (9.2)**	**3 (3.4)**
Baseline: Biochemical Hy's Law Range						
Normal Range	0	0	0	0	0	0
Near Normal	0	0	0	0	0	0
Temple's Corollary Range	0	0	0	0	0	0
Cholestasis Range	1 (0.6)	1 (0.6)	0	0	1 (1.0)	1 (1.1)
Biochemical Hy's Law Range	**9 (5.4)**	**6 (3.6)**	**1 (1.5)**	**1 (1.2)**	**8 (8.2)**	**5 (5.7)**

eDISH=evaluation of drug-induced serious hepatotoxicity; OCA=obeticholic acid; USPI=United States Prescribing Information

Note: In Study 302, 185 (55%) patients were contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

8.3.5.1.3. Adjudication of Potential Liver Injury Events in Study 302

In Study 302, a broad set of hepatic trigger events (based on Investigator-reported TEAEs and pre-specified lab thresholds) were adjudicated by an expert, independent DILI committee (e.g., HSAC) to evaluate for potential liver injury and then determine severity and causality to investigational product in a blinded manner. The committee used the criteria outlined in the tables below to provide a blinded causality and severity assessment.

Hepatic Injury Potential:

Category	Descriptor
No Evidence of Liver Injury	Lab error Other explanation (e.g., muscle injury)
Potential Evidence for Liver Injury	There is potential evidence for a liver injury.

Severity Assessment:

Severity Rating	Descriptor
Mild Hepatic Injury	There are elevations in serum ALT and/or Alk P levels, but the total serum bilirubin level is <2.5mg/dL, and INR is <1.5
Moderate Hepatic Injury	There are elevations in serum ALT and/or Alk P levels, but the total serum bilirubin level is ≥2.5mg/dL, and INR is ≥1.5
Moderate-Severe Hepatic Injury	There are elevations in serum ALT and/or Alk P, and bilirubin or INR levels, and hospitalization or ongoing hospitalization is prolonged because of a DILI episode
Severe Hepatic Injury	There are elevations in serum ALT and/or Alk P levels, and there is at least one of the following: - Hepatic failure (INR ≥1.5, ascites, or encephalopathy) - Other organ failure believed to be due to a DILI event (i.e., renal or pulmonary)
Fatal Case	Death or liver transplantation from a DILI event

Causality:

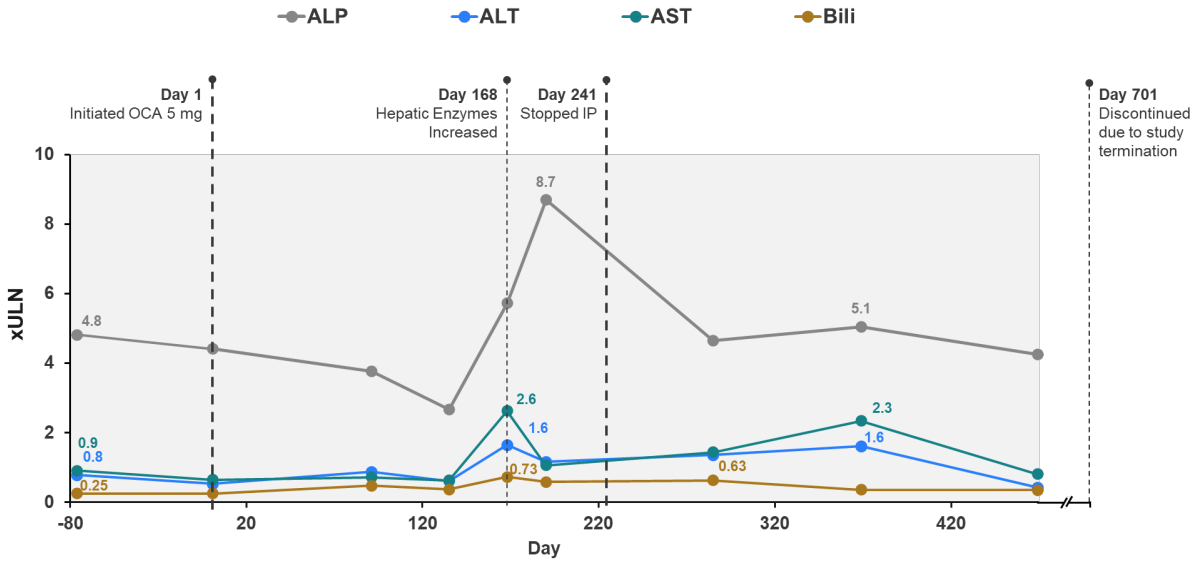
Score	Descriptor	Details
Insufficient Information	Insufficient details in case package to make any assessment	Cases that do not have enough information provided to be assigned one of the below 4 categories, will be designated as having insufficient information. Members will be asked to specify what additional information is required to complete the causality assessment.
Unlikely drug related	Confidence of causality assessment is <25%	A role for study drug is unlikely based on the available information. Another etiology is likely to be the cause of injury.

Score	Descriptor	Details
Possible drug related	Confidence of causality assessment is between 25% to 49%	The available evidence does not definitively exclude the possibility of a causal role for study drug, but another etiology is more likely to be the cause of injury.
Probable drug related	Confidence of causality assessment is between 50% to 74%	Causality is supported by the preponderance of evidence; the drug is more likely to be the causal agent rather than not. Testing rules out some/most other likely causes.
Highly likely drug related	Confidence of causality assessment is between 75% to 100%	The evidence is beyond a reasonable doubt (positive rechallenge)

In the USPI indicated population of Study 302, there were no potential liver injury events assessed as highly likely related or probably related to investigational product by the HSAC across treatment groups. A total of 5 patients had a potential liver injury event assessed as possibly related to investigational product by the HSAC (4 patients in the OCA group and 1 patient in the placebo group; Figure 39, Figure 40, Figure 41, Figure 42, and Figure 43).

Across both treatment groups in the USPI indicated population, possibly related potential liver injury events occurred within the first 3 to 4 months of starting investigational product and were appropriately managed (i.e., resolved or returned to baseline status) with discontinuation of investigational product and any confounding hepatotoxic medications such as rifampicin.

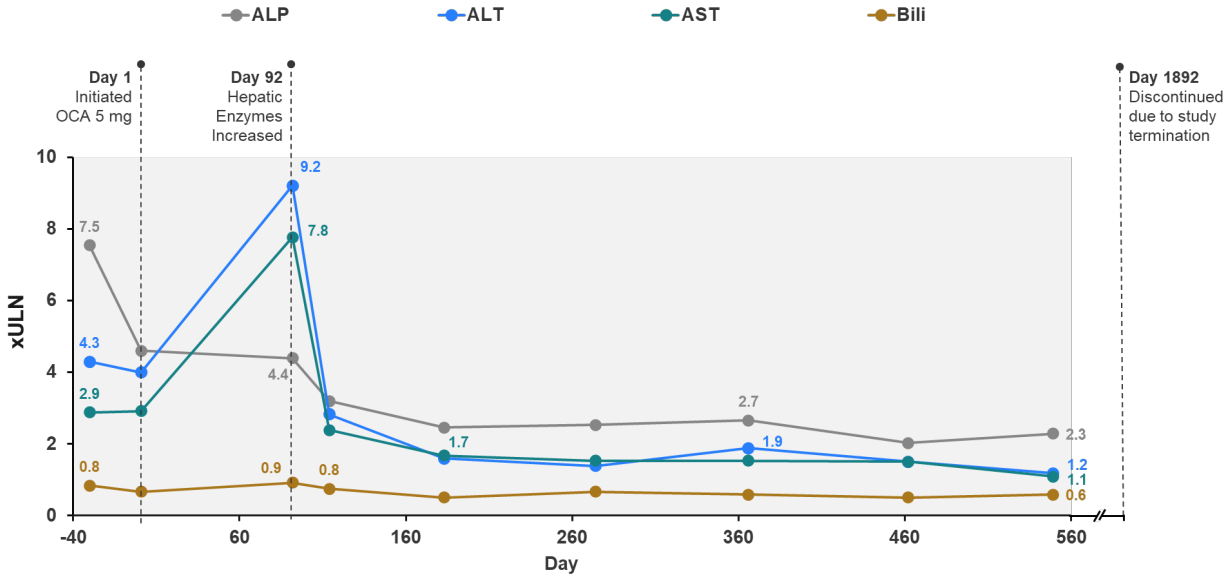
Figure 39: Study 302 – Patient OCA1 (69-year-old White Female, OCA-treated, Mild Potential Hepatic Liver Injury)



Bili=bilirubin; IP=investigational product; OCA=obeticholic acid

Patient OCA1: 69-year-old female in the OCA group was found to have a persistent elevation of ALP (lab trigger: ALP >1000 U/L and >15% increase from baseline) on Study Day 91 with a lesser degree of total bilirubin and ALT elevation. OCA dose was reduced to 10 mg every other day on Study Day 135. ALP remained persistently elevated, and OCA was withdrawn on Study Day 241 due to pruritus and rising liver biochemistries starting on Day 168. There was improvement from peak ALP after OCA withdrawal, serum ALP did return to near baseline but remained >1000 U/L. There was no associated synthetic liver function abnormality.

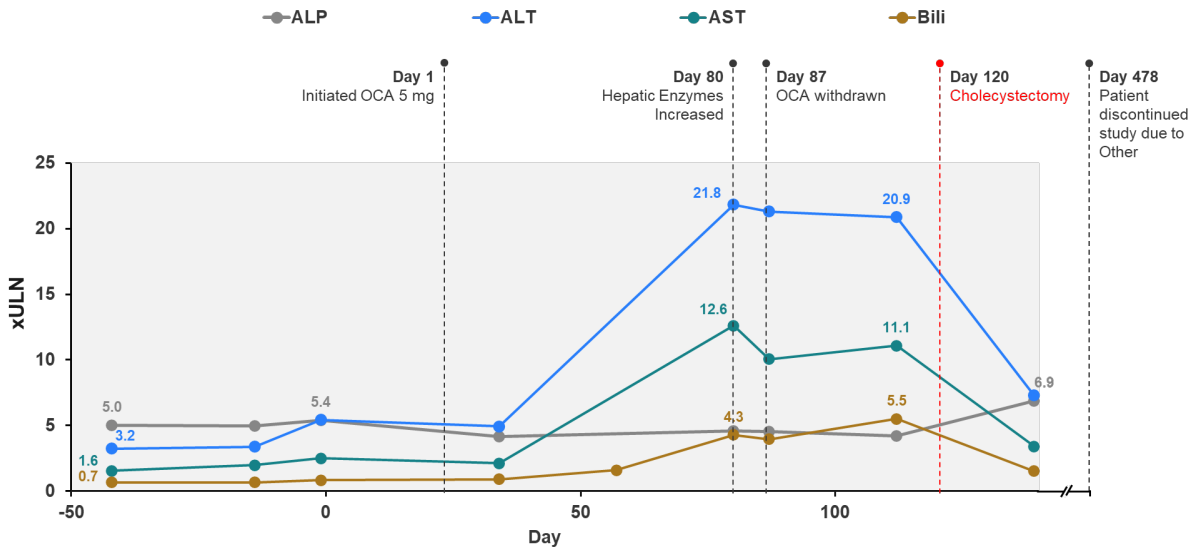
Figure 40: Study 302 – Patient OCA2 (41-year-old American Indian or Alaska Native Female, OCA-treated, Mild Potential Hepatic Liver Injury)



Bili=bilirubin; IP=investigational product; OCA=obeticholic acid

Patient OCA2: 41-year-old female in the OCA group experienced a single occasion of elevated ALT, AST (lab trigger: ALT/AST >3x baseline and >5x ULN), and GGT, without total bilirubin or ALP changes on Study Day 92. The patient continued on OCA without dosing interruptions, and subsequent labs on Study Day 114 returned to baseline values and continued to improve over time until the end of study (due to study termination) on Study Day 1893. The patient was also diagnosed with celiac disease on Study Day 462.

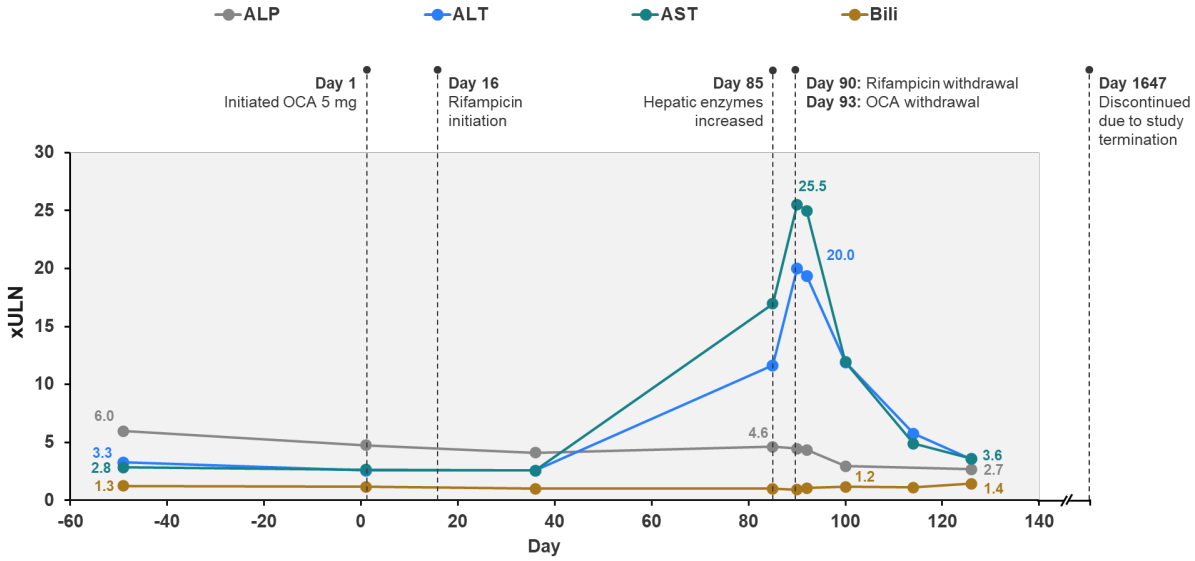
Figure 41: Study 302 – Patient OCA3 (45-year-old White Female, OCA-treated, Moderate Potential Hepatic Liver Injury)



Bili=bilirubin; IP=investigational product; OCA=obeticholic acid

Patient OCA3: 45-year-old female in the OCA group was found to have elevations in liver biochemistries (trigger: ALT and AST >5x ULN and total bilirubin >3x ULN) on Study Day 80. The patient had been diagnosed by ultrasound with cholelithiasis on Day 49, without documentation of biliary symptoms in association. Investigational product was stopped on Study Day 87 and the patient eventually underwent a laparoscopic cholecystectomy on Study Day 121. On Study Day 139, liver biochemistries had improved significantly; no further blood tests were available for review due to withdrawal of consent, but the patient agreed to continue participation in the study until Day 478. The patient was also taking ibuprofen and simvastatin at the time of the event.

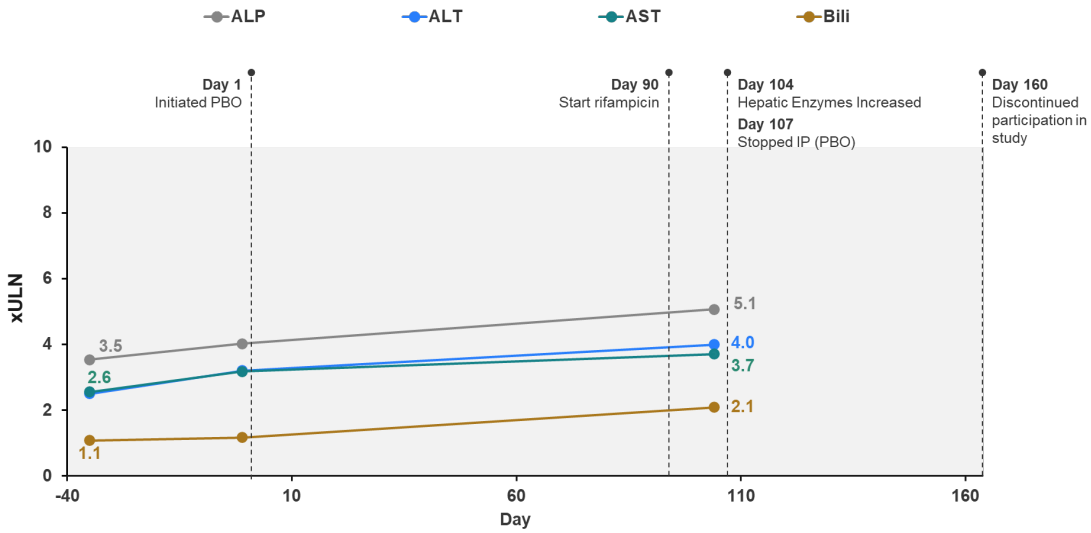
Figure 42: Study 302 – Patient OCA4 (57-year-old White Female, OCA-treated, Moderate-severe Potential Hepatic Liver Injury)



Bili=bilirubin; IP=investigational product; OCA=obeticholic acid

Patient OCA4: 57-year-old female in the OCA group was found to have predominantly elevated transaminases (lab trigger: ALT and AST >5x baseline) on Study Day 92. Concomitant and potential hepatotoxic medication included rifampicin, which had been initiated on Study Day 16. Both the rifampicin and investigational product were stopped, and the patient was admitted for a liver biopsy; histology results were consistent with chronic PBC. Synthetic liver function remained normal. Elevated transaminases returned to baseline approximately 1 month after withdrawal of rifampicin and OCA. The Investigator assessed the cause of the potential liver injury event to be most likely rifampicin.

Figure 43: Study 302 – Patient PBO1 (44-year-old White Female, Placebo, Moderate Potential Hepatic Liver Injury)



Bili=bilirubin; IP=investigational product; OCA=obeticholic acid

Patient PBO1: 44-year-old female in the placebo group experienced an elevation of predominantly GGT (479 U/L from baseline value of 261 U/L) and total bilirubin (2.5 mg/dL from baseline value of 1.4 mg/dL) with more modest elevation of ALT, AST, and ALP on Study Day 104. Investigational product was discontinued. Concomitant medications included rifampicin at the time of the event, which was discontinued on Day 118. Laboratory results after Study Day 104 were unavailable.

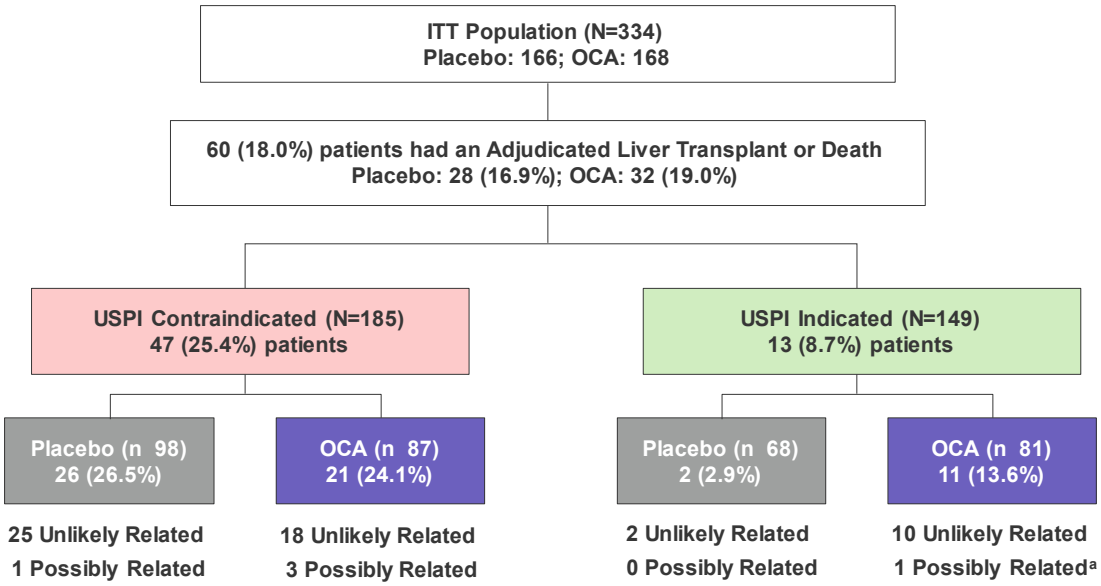
8.3.5.1.4. Liver Transplants and Deaths in Study 302

In Study 302, liver transplants and deaths were captured as part of the efficacy endpoints in the ITT analyses. As the ITT analyses could not provide an unbiased estimate of efficacy due to treatment crossover and functional unblinding, Intercept conducted a patient-level review of the cases within the current USPI indicated population to assess for safety. All hepatic outcomes, including liver transplants and deaths, were adjudicated by an independent, expert committee (HSAC) for causality.

A total of 60 patients (32 [19%] in the OCA group and 28 [17%] in the placebo group) had a liver transplant or death that occurred during the study; with a total of 13 patients within the UPSI indicated population (11 [14%] in the OCA group and 2 [3%] in the placebo group) (Figure 44). The 13 events of liver transplant and death within the USPI indicated population are outlined in Table 9 (1 death), Table 10 (7 liver transplants and 1 death), and Table 11 (1 liver transplant and 3 deaths).

In the USPI indicated population (Figure 44), 1 patient in the OCA group and none in the placebo group had events that were assessed as possibly related to investigational product. Of note, the patient in the OCA group would be contraindicated per current USPI due to potential evidence of portal hypertension at baseline (ultrasound imaging with splenomegaly and an endoscopy report with “equivocal” esophageal varices reported by the Investigator). See Figure 45 for patient narrative.

Figure 44: Study 302 – Adjudicated Liver Transplants and Deaths (ITT Population)



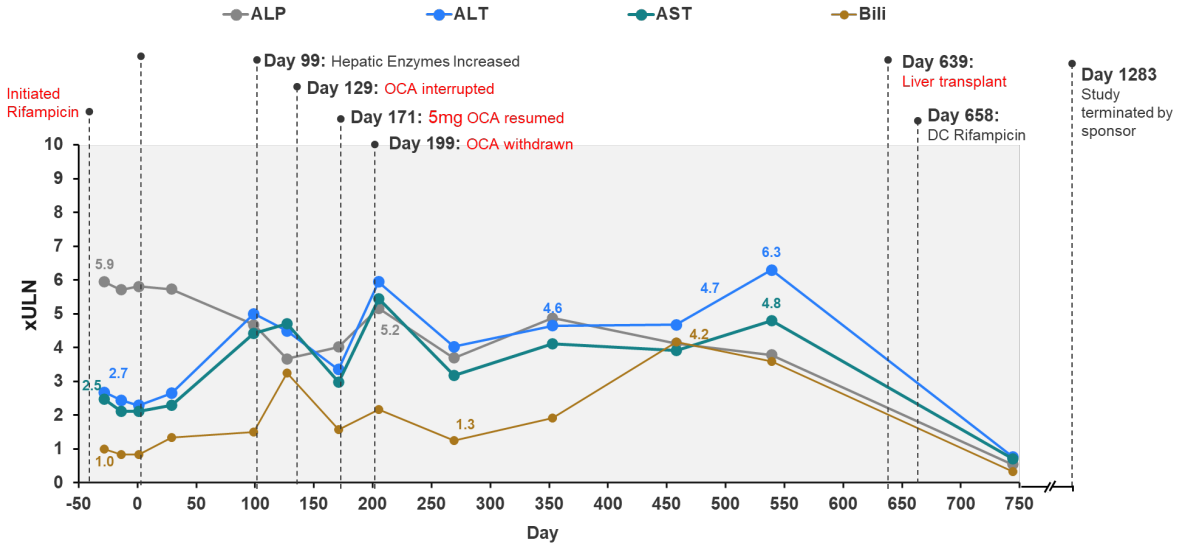
ITT=intent-to-treat; OCA=obeticholic acid; PH=portal hypertension; USPI=United States Prescribing Information

Note: Adjudicated liver transplants and deaths were captured as part of the efficacy endpoints in the ITT analyses. Therefore, analyses were conducted in the ITT Population (i.e., on-study).

Note: In Study 302, 185 (55%) patients would be contraindicated per the current USPI at baseline (i.e., advanced stage disease) and 149 (45%) patients were considered indicated per the current USPI at baseline (i.e., earlier stage disease). The subgroup analyses were programmed retrospectively using baseline data and may have been limited depending on the availability of the baseline data.

[a] One possibly related liver transplant had evidence of portal hypertension at baseline and would be contraindicated per current USPI (See Figure 45 for patient narrative).

Figure 45: Study 302 – Patient OCA6 (43-year-old White Female, OCA-treated, Possibly Related Liver Transplant)



Patient OCA6: 43-year-old female in the OCA group with biopsy proven stage 4 PBC, alcohol use disorder with pancreatic insufficiency, underwent an allogenic liver transplant on (b) (6) (b) (6) (Study Day 639), approximately 1 year and 3 months after the discontinuation of OCA. The patient had baseline evidence of splenomegaly with "equivocal" esophageal varices at baseline, suggesting potential evidence of portal hypertension which is a contraindication per current USPI. Investigational product had been permanently discontinued approximately 6 months after the initiation due to increases in ALT, AST, and bilirubin. Rifampicin use present at study entry was considered as a confounder. The patient experienced disease progression and eventually underwent liver transplantation on Day 639, after which the rifampicin was discontinued.

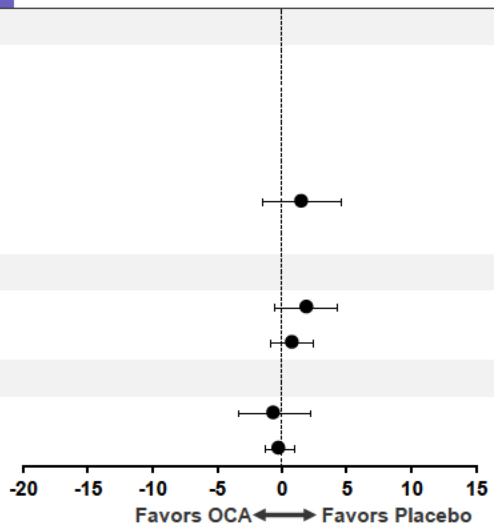
8.3.5.2. Cardiovascular

8.3.5.2.1. Exposure-adjusted Incidence Rates

While there was an imbalance in crude incidence for Study 302, based on the totality of evidence, the data do not support an excess risk for CV AEs in OCA-treated patients with PBC compared to placebo. In Study 302, the exposure-adjusted risk difference was 0.8 per 100 PYs for serious CV events with a CI including zero. In Study 405, the exposure-adjusted risk difference was -0.2 per 100 PYs for serious CV events, with a CI that includes zero.

Table 28: Investigator-reported Cardiovascular Events per 100 Patient Years in Studies 301, 302, and 405 (Safety Population)

	Placebo IRY	OCA IRY	IRY Difference (95% CI)
Study 301			
OCA 5→10 mg	**N=73[a]**	**N=70**	
TEAEs	0	0	NE
Serious AEs	0	0	NE
OCA 10 mg	**--**	**N=73**	
TEAEs	0	1.5	1.5 (-1.5, 4.5)
Serious AEs	0	0	NE
Study 302	**N=166**	**N=168**	
TEAEs	2.0	3.9	1.9 (-0.5, 4.3)
Serious AEs	0.9	1.7	0.8 (-0.8, 2.4)
Study 405	**N=405.4[b]**	**N=403**	
TEAEs	7.5	7.0	-0.6 (-3.3, 2.2)
Serious AEs	1.6	1.4	-0.2 (-1.3, 0.9)



AE=adverse event; IRY=number of patients with event per 100 patient years; NE=not estimable; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; TEAE=treatment-emergent adverse event

[a] One placebo group evaluated in Study 301.

[b] Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group; serious AEs were defined as events that led to death and/or hospitalization.

8.3.5.2.2. Adjudicated Cardiovascular Events

For Study 302, all suspected MACE, including CV-related death, non-fatal myocardial infarction, non-fatal stroke, and additional CV events were adjudicated by an independent, expert committee in a blinded fashion (Cardiac Outcomes Committee).

The risk adjusted rates were low with 95% CIs including zero and no meaningful difference observed between OCA and placebo, as adjudicated by the Cardiac Outcomes Committee (Table 29). The one adjudicated CV-related death occurred in a 61-year-old female patient due to a hemorrhagic (sub-arachnoid) cerebrovascular accident on Day 348; this patient had evidence of underlying portal hypertension (esophageal varices) at baseline and would now be contraindicated to Ocaliva based on the current USPI.

Table 29: Adjudicated Cardiovascular Events per 100 Patient Years in Study 302 (Safety Population)

	Placebo N=166 n (%) [IRY]	OCA N=168 n (%) [IRY]	IRY Difference (95% CI)
Patient with at least 1 Adjudicated CV Events	**3 (1.8) [0.9]**	**5 (3.0) [1.2]**	**0.3 (-1.1, 1.8)**
Revascularization procedure	0	2 (1.2) [0.5]	0.5 (-0.2, 1.1)
Stroke	0	2 (1.2) [0.5]	0.5 (-0.2, 1.1)
Cardiovascular Death	0	1 (0.6) [0.2]	0.2 (-0.2, 0.7)
Myocardial Infarction	0	1 (0.6) [0.2]	0.2 (-0.2, 0.7)
Arrythmia	1 (0.6) [0.3]	0	-0.3 (-0.8, 0.3)
Heart Failure	2 (1.2) [0.6]	0	-0.6 (-1.3, 0.2)

CV=cardiovascular; IRY=number of patients with event per 100 patient years; OCA=obeticholic acid

8.3.5.3. Dyslipidemia

There is no excess risk in dyslipidemia events with OCA use in patients with PBC compared to placebo from Studies 301, 302, and 405 (Table 30 and Table 31).

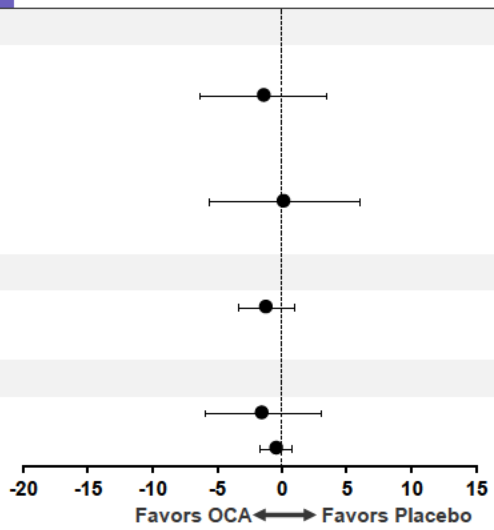
Table 30: Dyslipidemia Events in Studies 301, 302, and 405 (Safety Population)

	Study 301 (Double-blind)			Study 302		Study 405	
n (%)	**Placebo N=73**	**OCA 5→10 mg N=70**	**OCA 10 mg N=73**	**Placebo N=166**	**OCA N=168**	**Weighted Non-OCA-treated N=405.4**	**Weighted OCA N=403**
Dyslipidemia TEAE	2 (2.7)	1 (1.4)	2 (2.7)	9 (5.4)	6 (3.6)	97.3 (24.0)	69 (17.1)
Serious AEs	0	0	0	0	0	14.3 (3.5)	8 (2.0)

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Note: For Study 405, serious AEs were defined as events that led to death and/or hospitalization.

Table 31: Dyslipidemia Events per 100 Patient Years in Studies 301, 302, and 405 (Safety Population)

	Placebo IRY	OCA IRY	IRY Difference (95% CI)
Study 301			
OCA 5→10 mg	**N=73[a]**	**N=70**	
TEAEs	2.9	1.5	-1.4 (-6.3, 3.5)
Serious AEs	0	0	NE
OCA 10 mg	**--**	**N=73**	
TEAEs	2.9	3.1	0.2 (-5.6, 6.1)
Serious AEs	0	0	NE
Study 302	**N=166**	**N=168**	
TEAEs	2.7	1.5	-1.2 (-3.3, 0.9)
Serious AEs	0	0	NE
Study 405	**N=405.4[b]**	**N=403**	
TEAEs	16.3	14.8	-1.5 (-6.0, 3.0)
Serious AEs	1.9	1.5	-0.4 (-1.7, 0.8)



AE=adverse event; IRY=number of patients with event per 100 patient years; NE=not estimable; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; TEAE=treatment-emergent adverse event

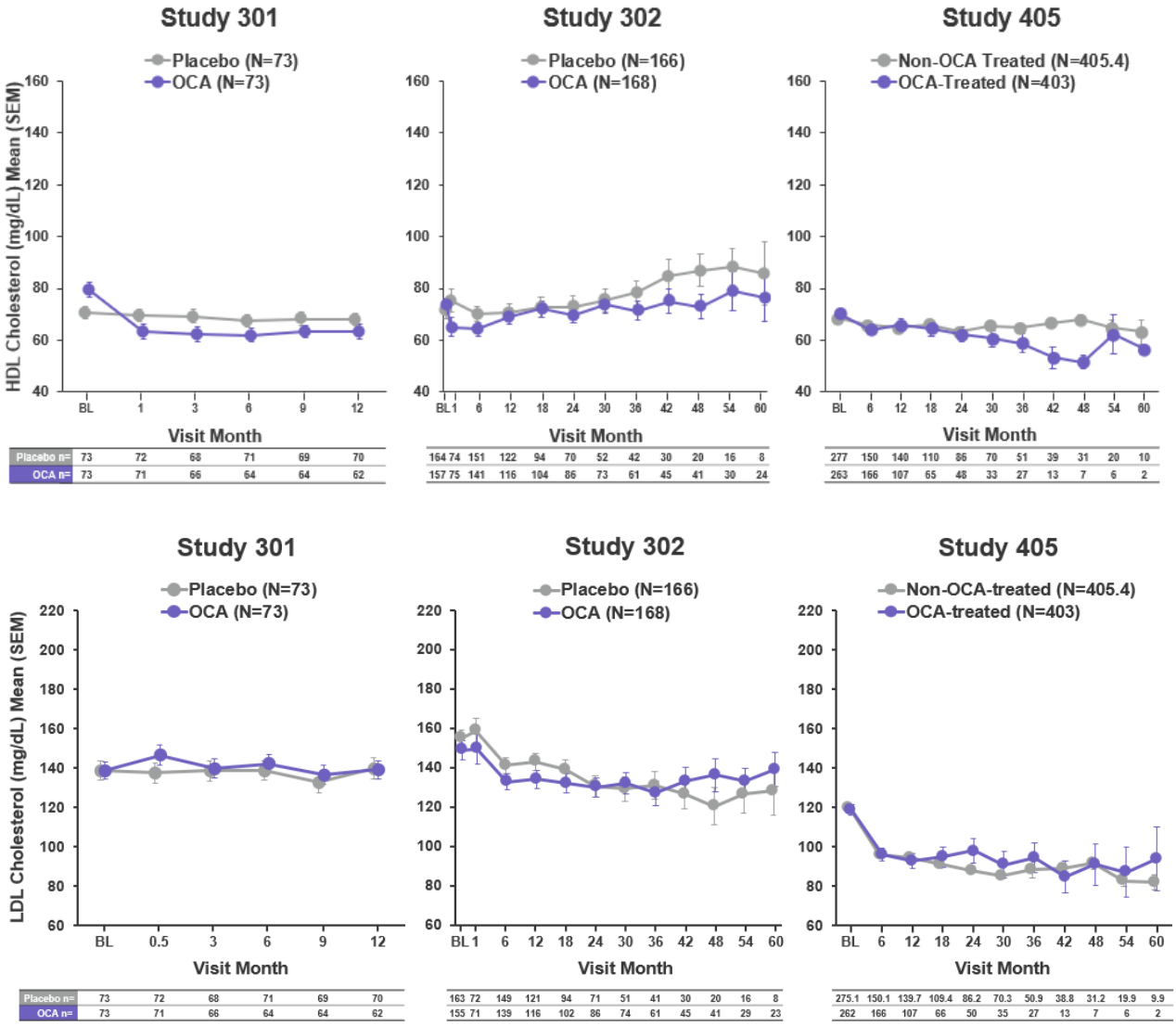
[a] One placebo group evaluated in Study 301.

[b] Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group; serious AEs were defined as events that led to death and/or hospitalization.

8.3.5.3.1. Serum HDL and LDL

In Studies 301, 302, and 405, mean baseline high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were elevated, which is consistent with background lipoprotein profiles in patients with PBC due to underlying chronic cholestatic disease (Lindor 2019). Importantly, this established dyslipidemia has not been shown to translate into increased CV events in patients with PBC (Suraweera 2018). Across the clinical studies including RWE, minimal differences were observed in serum lipoproteins overtime for patients on OCA compared to patients on placebo (Figure 46). The modest reductions in serum HDL observed with OCA trended toward baseline levels overtime and stayed within normal limits at all timepoints tested.

Figure 46: Mean Serum HDL and LDL Overtime



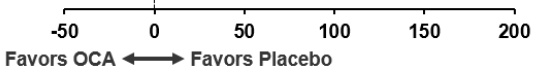
HDL=high-density lipoprotein; LDL=low-density lipoprotein; OCA=obeticholic acid; SEM=standard error of mean
For Study 301, OCA = OCA 10 mg.

8.3.5.4. Pruritus

Pruritus EAIRs are summarized in Table 32. The incidence of pruritus was significantly lower in the Study 405 due to the nature of under-reporting of certain events such as pruritus in claims data versus clinical trials, and this observation is consistent with a meta-analysis of real-world studies examining pruritus in OCA-treated patients (Horne 2022). In Study 405, concomitant anti-pruritic medication use was higher in the OCA group compared to the placebo group.

Table 32: Pruritus Events per 100 Patient Years in Studies 301, 302, and 405

	Placebo IRY	OCA IRY	IRY Difference (95% CI)
Study 301			
OCA 5→10 mg	**N=73[a]**	**N=70**	
TEAEs	57.2	106.7	49.5 (9.9, 89.2)
Serious AEs	0	0	NE
OCA 10 mg	**--**	**N=73**	
TEAEs	57.2	186.4	129.2 (73.8, 184.6)
Serious AEs	0	0	NE
Study 302	**N=166**	**N=168**	
TEAEs	39.9	103.9	64.0 (44.4, 83.6)
Serious AEs	0	0.5	0.5 (-0.2, 1.1)
Study 405	**N=405.4[b]**	**N=403**	
TEAEs	6.4	7.9	1.5 (-1.6, 4.7)
Serious AEs	0.7	0	NE



AE=adverse event; IRY=number of patients with event per 100 patient years; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; TEAE=treatment-emergent adverse event

[a] One placebo group evaluated in Study 301.

[b] Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group; serious AEs were defined as events that led to death and/or hospitalization.

8.3.5.5. Gallbladder/Gallstone

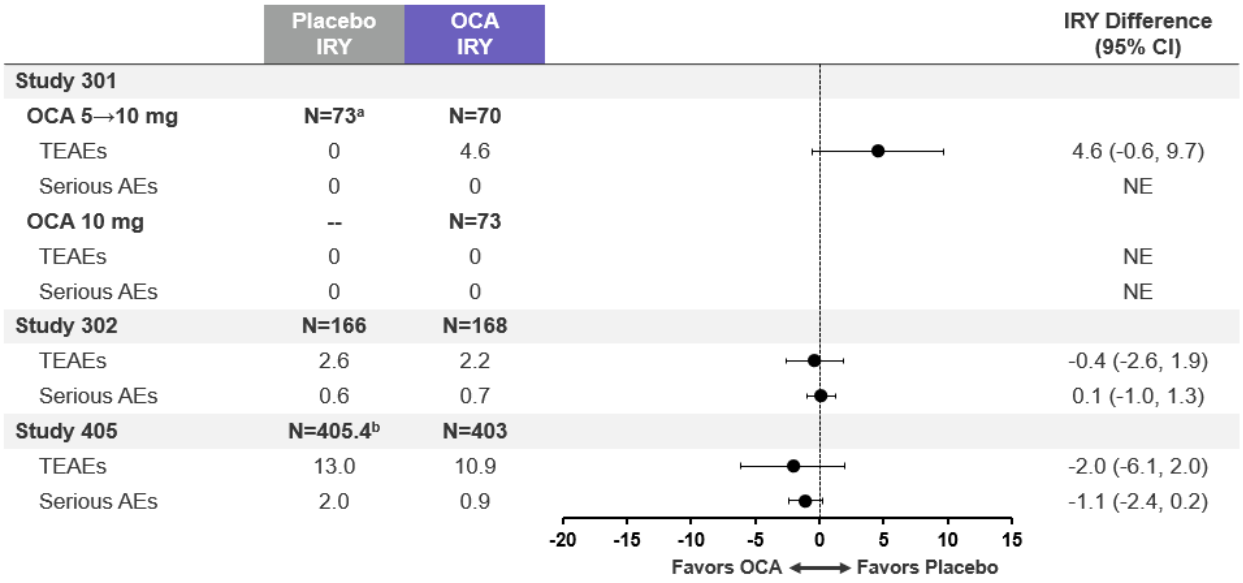
In totality, the data do not support an excess risk for gallbladder/gallstone AEs in OCA-treated patients with PBC compared to placebo (Table 33 and Table 34). In Study 301, the exposure-adjusted risk difference was 4.6 PYs for overall TEAEs in the OCA titration (5mg →10 mg) group with a 95% CI including zero. There was no calculable difference observed for SAEs in the titration group and no calculable difference observed in the OCA 10 mg for TEAEs or SAEs. Both Studies 302 and 405 had exposure-adjusted risk differences near zero with CIs including zero for overall and SAEs. In addition, since accelerated approval in 2016, Ocaliva has been contraindicated in patients with biliary obstruction and treatment should be interrupted until complete resolution of the event per the USPI.

Table 33: Gallbladder/Gallstone Events in Studies 301, 302, and 405 (Safety Population)

n (%)	Study 301 (Double-blind)			Study 302		Study 405	
	Placebo N=73	OCA 5→10 mg N=70	OCA 10 mg N=73	Placebo N=166	OCA N=168	Weighted Non-OCA-treated N=405.4	Weighted OCA N=403
Gallbladder/ gallstone TEAE	0	3 (4.3)	0	9 (5.4)	9 (5.4)	82.5 (20.4)	54 (13.4)
Serious AEs	0	0	0	2 (1.2)	3 (1.8)	15.1 (3.7)	5.1 (1.2)

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Note: For Study 405, serious AEs were defined as events that led to death and/or hospitalization.

Table 34: Gallbladder/Gallstone Events per 100 Patient Years in Studies 301, 302, and 405 (Safety Population)



AE=adverse event; IRY=number of patients with event per 100 patient years; NE=not estimable; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; TEAE=treatment-emergent adverse event
[a] One placebo group evaluated in Study 301.
[b] Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group; serious AEs were defined as events that led to death and/or hospitalization.

8.3.5.6. Renal

Based on the totality of evidence, there was no excess risk of renal events with OCA use in patients with PBC compared to placebo (Table 35 and Table 36). Exposure-adjusted risk differences are near zero with 95% CIs including zero, except for Study 405 which is in favor of OCA therapy.

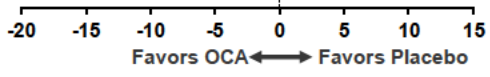
Table 35: Renal Events in Studies 301, 302, and 405

	Study 301 (Double-blind)			Study 302		Study 405	
n (%)	Placebo N=73	OCA 5→10 mg N=70	OCA 10 mg N=73	Placebo N=166	OCA N=168	Weighted Non-OCA-treated N=405.4	Weighted OCA N=403
Renal TEAE	2 (2.7)	2 (2.9)	1 (1.4)	13 (7.8)	17 (10.1)	85.6 (21.1)	45 (11.2)
Serious AEs	0	0	0	2 (1.2)	4 (2.4)	23 (5.8)	8 (2.0)

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Note: For Study 405, serious AEs were defined as events that led to death and/or hospitalization.

Table 36: Renal Events per 100 Patient Years in Studies 301, 302, and 405

	Placebo IRY	OCA IRY	IRY Difference (95% CI)
Study 301			
OCA 5→10 mg	**N=73[a]**	**N=70**	
TEAEs	2.9	3.0	0.1 (-5.7, 5.9)
Serious AEs	0	0	NE
OCA 10 mg	**--**	**N=73**	
TEAEs	2.9	1.5	-1.4 (-6.4, 3.6)
Serious AEs	0	0	NE
Study 302	**N=166**	**N=168**	
TEAEs	3.8	4.2	0.4 (-2.5, 3.2)
Serious AEs	0.6	1.0	0.4 (-0.8, 1.6)
Study 405	**N=405.4[b]**	**N=403**	
TEAEs	13.4	8.9	-4.5 (-8.1, -1.0)
Serious AEs	3.1	1.4	-1.7 (-3.1, -0.3)



AE=adverse event; IRY=number of patients with event per 100 patient years; NE=not estimable; OCA=obeticholic acid; SMR=standardized mortality/morbidity ratio; TEAE=treatment-emergent adverse event
[a] One placebo group evaluated in Study 301.
[b] Study 405 utilized a SMR-weighted-OCA eligible but non-OCA-treated comparator group; serious AEs were defined as events that led to death and/or hospitalization.

8.3.6. Safety Topics from Open-label Study 301 LTSE

An overview of safety topics from Study 301 LTSE is presented in Table 37. Long-term exposure of up to an additional 5 years in patients with PBC was generally consistent with the exposure-adjusted risk differences in hepatic, CV, dyslipidemia, gallbladder/gallstone, renal, or pruritus AEs compared to the placebo-controlled clinical trials.

Table 37: Safety Topics in Study 301 LTSE

	OCA N=193	
	n (%)	IRY
Hepatic TEAEs	36 (18.7)	6.6
Serious AEs	3 (1.6)	0.5
CV TEAEs	8 (4.1)	1.3
Serious AEs	3 (1.6)	0.5
Dyslipidemia TEAEs	11 (5.7)	1.9
Serious AEs	0	0
Gallbladder/gallstone TEAEs	10 (5.2)	1.7
Serious AEs	2 (1.0)	0.3
Renal TEAEs	10 (5.2)	1.7
Serious AEs	0	0
Pruritus TEAEs	107 (55.4)	33.3
Serious AEs	0	0

AE=adverse event; IRY=number of patients with event per 100 patient years; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

8.4. Appendix D: Study 401 (Double-Blind, Placebo-controlled, Postmarketing Requirement)

Study 747-401: A Phase 4, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Pharmacokinetics and Safety of Obeticholic Acid in Patients with Primary Biliary Cholangitis and Moderate to Severe Hepatic Impairment

Patients with moderate or severe hepatic impairment are contraindicated per the current USPI; therefore, the data from this study are of limited value to prescribers for Ocaliva in PBC.

747-401 - Study Population

A total of 22 patients of the originally planned 50 patients were randomized in the study (10 patients in the OCA group and 12 in the placebo group) and comprised the Randomized, ITT, and Safety populations. Of these, 10 (45.5%) patients (6 patients in the OCA group and 4 patients in the placebo group) completed the DB Phase. The majority of patients were White (95.5%) and female (72.7%). The median age of patients was 63 (range: 45 to 79 years old).

In general, baseline characteristics, including Child Pugh (CP) and MELD scores, were well balanced across treatment arms. The majority of patients had CP Class B (100.0% [OCA] and 91.7% [placebo]) whereas 0.0% (OCA) and 8.3% (placebo) patients had CP Class C. Mean (SD) Baseline CP score was 7.7 (0.67) in the OCA and 7.9 (0.90) in the placebo groups. Mean (SD) Baseline MELD score was 12.7 (3.47) in the OCA and 12.4 (2.97) in the placebo groups. The mean (SD) age at time of consent was 60.5 (10.19) years in the OCA and 62.5 (9.10) years in the placebo groups, and the percentage of females was 60.0% (OCA) and 83.3% (placebo).

747-401 – PK Summary

Six patients with hepatic impairment (CP-B) were included in the PK analysis: 6 patients received OCA 5 mg once weekly, of which 4 patients were titrated to 5 mg twice weekly and of the 4 patients, 2 patients were titrated to 10 mg twice weekly. No patients with severe hepatic impairment (CP-C) were evaluable for PK assessment.

The PK results of this study were consistent with the simulation of total OCA exposure following OCA 5 mg once weekly dose regimen. The observed mean $AUC_{0\text{-}24h}$ for total OCA at Week 12 (i.e., steady-state) was 2970 ng·h/mL comparable to the simulated predicted mean $AUC_{0\text{-}24h}$ of 2633 ng·h/mL (data on file); these exposures are comparable to the observed total OCA exposure ($AUC_{0\text{-}24h}$=2762 ng·h/mL) following an OCA 10 mg daily dose in patients without hepatic impairment. Based on these PK results, the initial dose of OCA 5 mg once weekly achieved targeted OCA exposure. Dose proportional increases in total OCA exposure were observed with dose titration from 5 mg once weekly to 5 mg twice weekly and 10 mg twice weekly.

747-401 – Efficacy Summary

Study 747-401 was not designed to detect differences in efficacy. OCA demonstrated no clear clinical benefit in this advanced PBC population (CP-B or CP-C) who are contraindicated per the USPI. No clinically meaningful differences were noted between OCA versus placebo for the composite outcome of death, including liver-related death, liver transplant, MELD, uncontrolled ascites, and hospitalizations for decompensating events. There was also no significant difference

between OCA and placebo for individual components of the composite outcome, except for variceal bleeding (unclear relevance given the small sample size).

There was a trend toward improving liver stiffness measurements over time among OCA versus placebo patients, however, because of the small sample size and a large standard error of the mean, the significance of this observation is unclear. Overall, change and percent change in liver stiffness (as assessed by TE) and enhanced liver fibrosis (ELF) were not statistically different than placebo.

Overall changes in total bile acids, total endogenous bile acids, fibroblast growth factor-19 and 7α-hydroxy-4-cholesten-3-one concentrations were observed in the OCA group over time; however, these were not clinically significant at any timepoint. Interpretation of these results is limited due to the small sample size and the study was not designed to detect outcome differences.

747-401 - Safety Summary

In the DB Phase and DB Extension Phase, the overall mean duration of exposure to study treatment was 296.5 days in the OCA and 233.4 days in the placebo groups. In the Safety Population, all patients in the OCA and placebo groups reported at least 1 TEAE during the DB Phase and DB Extension Phase of the study. The most frequently reported TEAEs (≥30%) were ascites, esophageal varices hemorrhage, pneumonia, urinary tract infection, pruritus, and anemia.

The majority of TEAEs in both treatment groups were reported to be mild (Grade 1) or moderate (Grade 2) in severity.

Study treatment or study discontinuations occurred in 5 (50.0%) patients in the OCA and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) patients in the OCA and 4 (33.3%) patients in the placebo group. The most common TEAE leading to study treatment interruption was ascites (2 [20.0%] patients in OCA and 1 [8.3%] in placebo groups).

A total of 7 (70.0%) patients in the OCA and 9 (75.0%) patients in the placebo groups experienced SAEs. In general, the nature of SAEs was consistent with the underlying advanced liver disease in this patient population.

A total of 5 deaths were reported (3 patients in the placebo group [hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal carcinoma] and 2 patients in the OCA group [multiple organ dysfunction syndrome and cardiac arrest]), which were all considered by the Investigator as not related or unlikely related to the study treatment. The case of death from clear cell renal cell carcinoma occurred within the study period; however, was reported after database lock.

Nine (90.0%) patients in the OCA and 9 (75.0%) patients in the placebo groups experienced an AE of special interest (AESI). Twenty subjects had 86 triggers that were identified for assessment for potential liver injury. Of these, 16 had no evidence of liver injury and the remaining 70 triggers were adjudicated as potential liver injury. The majority of the triggers were assessed as unlikely related to treatment by an independent HSAC, except for 2 cases (1 in the placebo arm and 1 in the OCA arm) were assessed as possibly related to study treatment.

No patients had clinically relevant abnormal ECG findings at Week 48 or DB Extension Month 12 across treatment groups.

Several mean baseline laboratory values were out of range, consistent with patients with PBC with moderate to advanced cirrhosis. These values did not change meaningfully over time following multiple dose administration of OCA or placebo; additionally, no meaningful discernable differences over time were noted between OCA and placebo.

There were no clinically relevant changes from baseline in vital signs (blood pressure, heart rate, temperature, and weight) in OCA group compared with placebo. No additional physical examination findings were observed, and no trends were detected.

747-401 Safety Summary

- Reported TEAEs were in general consistent with the known safety profile of OCA and anticipated for patients with advanced PBC disease.
- The most commonly reported TEAEs in OCA-treated patients were ascites, pruritus, anemia, esophageal varices hemorrhage, pneumonia, and urinary tract infection.
- The incidence of severe TEAEs was similar between placebo (58.3%) and OCA (60.0%) groups.
- The incidence of SAEs was similar among both treatment arms (75% in placebo and 70% in OCA). There were 5 deaths in the study (3 in placebo-treated patients: hepatic encephalopathy, aortic aneurysm rupture, and clear renal cell carcinoma; and 2 in OCA-treated patients: multiple organ dysfunction syndrome and cardiac arrest). All deaths were assessed by the Investigator as not related/unlikely related to the study treatment.
- Based on a broad set of highly sensitive pre-specified triggers, a total of 20 patients had events assessed as potential hepatic injury for further assessment of causality to drug and event severity. Two patients (one placebo, one OCA) had events assessed as possibly related to study treatment. The remaining 18 patients experienced events assessed as unlikely related to investigational product.

747-401 – Overall Conclusions

At the time of Ocaliva approval in May 2016, there were limited clinical data available for OCA treatment in patients with PBC suffering from more advanced liver disease. Results from previous Phase 1 and 2 studies showed doses of OCA administered to patients with moderate or severe hepatic impairment should be lower than those for patients with normal hepatic function to achieve similar hepatic exposure. Thus, the initial labelling included a weekly dosing regimen for PBC patients with moderate (CP-B) and severe (CP-C) hepatic impairment of 5 mg twice weekly (at least 3 days apart between doses) and subsequently to 10 mg twice weekly (at least three days apart between doses) depending on response and tolerability.

Patient recruitment and retention in Study 747-401 were challenging given the availability of marketed Ocaliva was a significant disincentive to patients with progressive liver disease to take part in a placebo-controlled study.

Following Ocaliva approval, it became clear that patients with CP-B or CP-C cirrhosis were not appropriate for Ocaliva treatment due to the increased risk of hepatic failure/decompensation

events, including fatal cases observed in clinical trials and postmarketing experience. In 2021, the USPI was revised to contraindicate use of OCA in patients with decompensated cirrhosis or a prior decompensation event and those with compensated cirrhosis with evidence of portal hypertension.

Notably, all patients who were enrolled in Study 747-401 would meet the revised contraindicated criteria of both the USPI.

The safety profile of OCA was consistent with that expected in a PBC patient population with moderate to advanced cirrhosis. The high incidence of TEAEs and serious TEAEs in this advanced patient population reinforce the contraindications in the USPI.

8.5. Appendix E: OCALIVA® PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OCALIVA® safely and effectively. See full prescribing information for OCALIVA.

OCALIVA® (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: HEPATIC DECOMPENSATION AND FAILURE IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS
See full prescribing information for complete boxed warning

- **Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in primary biliary cholangitis (PBC) patients with either compensated or decompensated cirrhosis. (5.1)**
- **OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension. (4)**
- **Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment. (2.3, 5.1)**

INDICATIONS AND USAGE

OCALIVA, a farnesoid X receptor (FXR) agonist, is indicated for the treatment of adult patients with primary biliary cholangitis (PBC)

- without cirrhosis or
- with compensated cirrhosis who do not have evidence of portal hypertension,

either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients 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. (1)

DOSAGE AND ADMINISTRATION

Recommended Dosage Regimen

The recommended starting dosage of OCALIVA, for PBC patients without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or who are intolerant to UDCA follows below:

- Start with a dosage of 5 mg once daily for the first 3 months.
- After the first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating OCALIVA, increase to a maximum dosage of 10 mg once daily. (2.2)

Routinely monitor patients during OCALIVA treatment for biochemical response, tolerability, and progression of PBC. (2.3)

Management of Patients with Intolerable Pruritus

- See full prescribing information for management options. (2.4)

Administration Instructions

- Take with or without food. (2.5)
- For patients taking bile acid binding resins, take OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible. (7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg (3)

CONTRAINDICATIONS

- decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (4)
- compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) (4)
- complete biliary obstruction (4)

WARNINGS AND PRECAUTIONS

- Hepatic Decompensation and Failure in PBC Patients with Cirrhosis: Routinely monitor patients for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessments. Closely monitor patients at risk of hepatic decompensation. Permanently discontinue in patients who develop laboratory or clinical evidence of hepatic decompensation; have compensated cirrhosis and develop evidence of portal hypertension; experience clinically significant hepatic adverse reactions; or develop complete biliary obstruction. Interrupt treatment in patients with severe intercurrent illness. (2.3, 4, 5.1)
- Severe Pruritus: Management strategies include the addition of bile acid binding resins or antihistamines; OCALIVA dosage reduction and/or temporary dosing interruption. (2.4, 5.2)
- Reduction in HDL-C: Monitor for changes in serum lipid levels during treatment. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are: pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Warfarin: Potential for decreased INR; monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range. (7.2)
- CYP1A2 Substrates with Narrow Therapeutic Index (e.g., theophylline and tizanidine): Potential for increased exposure to CYP1A2 substrates; monitor drug concentrations of CYP1A2 substrates with narrow therapeutic index. (7.3)
- Inhibitors of Bile Salt Efflux Pump (e.g., cyclosporine): Avoid use. If concomitant use is necessary, monitor serum transaminases and bilirubin. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATIC DECOMPENSATION AND FAILURE IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS

- **Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in primary biliary cholangitis (PBC) patients with either compensated or decompensated cirrhosis *[see Warnings and Precautions (5.1)]*.**
- **OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension *[see Contraindications (4)]*.**
- **Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation; have compensated cirrhosis and develop evidence of portal hypertension; or experience clinically significant hepatic adverse reactions while on treatment *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

OCALIVA® is indicated for the treatment of adult patients with primary biliary cholangitis (PBC)

- without cirrhosis or
- with compensated cirrhosis who do not have evidence of portal hypertension,

either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP) *[see Clinical Studies (14)]*. 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Prior to the initiation of OCALIVA, healthcare providers should determine whether the patient has decompensated cirrhosis (e.g., Child-Pugh Class B or C), has had a prior decompensation event, or has compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) because OCALIVA is contraindicated in these patients *[see Contraindications (4), Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage Regimen

The recommended dosage of OCALIVA for PBC patients without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA *[see Clinical Studies (14)]* follows below:

- Start with a dosage of 5 mg once daily for the first 3 months.
- After the first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating OCALIVA, increase to a maximum dosage of 10 mg once daily.

2.3 Monitoring to Assess Safety, Need for OCALIVA Discontinuation

Routinely monitor patients during OCALIVA treatment for biochemical response, tolerability, and progression of PBC. Closely monitor patients with compensated cirrhosis, concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or severe intercurrent illness for new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) or increases above the upper limit of normal in total bilirubin, direct bilirubin, or prothrombin time. Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, experience clinically significant hepatic adverse reactions, or develop complete biliary obstruction *[see Contraindications (4), Warnings and Precautions (5.1)]*.

2.4 Management of Patients with Intolerable Pruritus on OCALIVA

For patients with intolerable pruritus on OCALIVA, consider one or more of the following management strategies:

- Add an antihistamine or bile acid binding resin *[see Dosage and Administration (2.5), Clinical Studies (14)]*.
- Reduce the dosage of OCALIVA to:
    - 5 mg every other day, for patients intolerant to 5 mg once daily.
    - 5 mg once daily, for patients intolerant to 10 mg once daily.
- Temporarily interrupt OCALIVA dosing for up to 2 weeks. Restart at a reduced dosage.

For patients whose dosage is reduced or interrupted, titrate the dosage based on biochemical response and tolerability *[see Dosage and Administration (2.2)]*.

Consider discontinuing OCALIVA treatment in patients who continue to experience persistent, intolerable pruritus despite management strategies *[see Warnings and Precautions (5.2)]*.

2.5 Administration Instructions

- Take OCALIVA with or without food.

- For patients taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible *[see Drug Interactions (7.1), Clinical Studies (14)]*.

3 DOSAGE FORMS AND STRENGTHS

OCALIVA is available as:

- 5 mg tablet: Off white to yellow, round tablet debossed with "INT" on one side and "5" on the other side.
- 10 mg tablet: Off white to yellow, triangular tablet debossed with "INT" on one side and "10" on the other side.

4 CONTRAINDICATIONS

OCALIVA is contraindicated in patients with:

- decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event *[see Warnings and Precautions (5.1)]*.
- compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) *[see Warnings and Precautions (5.1)]*.
- complete biliary obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Decompensation and Failure in PBC Patients with Cirrhosis

Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in PBC patients with cirrhosis, either compensated or decompensated. Among postmarketing cases reporting it, median time to hepatic decompensation (e.g., new onset ascites) was 4 months for patients with compensated cirrhosis; median time to a new decompensation event (e.g., hepatic encephalopathy) was 2.5 months for patients with decompensated cirrhosis.

Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dosage for that patient population; however, cases of hepatic decompensation and failure have continued to be reported in patients with decompensated cirrhosis even when they received the recommended dosage.

Hepatotoxicity was observed in the OCALIVA clinical trials. A dose-response relationship was observed for the occurrence of hepatic adverse reactions including jaundice, worsening ascites, and primary biliary cholangitis flare with dosages of OCALIVA of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with OCALIVA in two 3-month, placebo-controlled clinical trials in patients with primarily early stage PBC *[see Overdosage (10)]*.

In a pooled analysis of three placebo-controlled clinical trials in patients with primarily early stage PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant hepatic adverse reactions, and isolated elevations in liver biochemical tests, per 100 patient exposure years (PEY) were: 5.2 in the OCALIVA 10 mg group (highest recommended dosage), 19.8 in the OCALIVA 25 mg group (2.5-times the highest recommended dosage) and 54.5 in the OCALIVA 50 mg group (5-times the highest recommended dosage) compared to 2.4 in the placebo group.

Patient Management

Routinely monitor patients for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessments to determine whether drug discontinuation is needed *[see Dosage and Administration (2.3)]*.

Closely monitor patients with compensated cirrhosis, concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or with severe intercurrent illness for new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) or increases above the upper limit of normal in total bilirubin, direct bilirubin, or prothrombin time to determine whether drug discontinuation is needed *[see Dosage and Administration (2.3)]*.

Permanently discontinue OCALIVA in patients who:

- develop laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy) *[see Contraindications (4)]*.
- have compensated cirrhosis and develop evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) *[see Contraindications (4)]*.
- experience clinically significant hepatic adverse reactions.
- develop complete biliary obstruction *[see Contraindications (4)]*.

If severe intercurrent illness occurs, interrupt treatment with OCALIVA and monitor the patient's liver function. After resolution of the intercurrent illness, consider the potential risks and benefits of restarting OCALIVA treatment.

5.2 Severe Pruritus

Severe pruritus was reported 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 in Trial 1, a 12-month double-blind randomized controlled clinical trial of 216 patients *[see Adverse Reactions (6.1)]*. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. In the subgroup of patients in the OCALIVA titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from Months 0 to 6 and 15% from Months 6 to 12. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration, and placebo arms, respectively.

Consider clinical evaluation of patients with new onset or worsening severe pruritus. Management strategies include the addition of bile acid binding resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing *[see Dosage and Administration (2.4)]*.

5.3 Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high-density lipoprotein-cholesterol (HDL-C). In Trial 1, dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At Month 12, the reduction from baseline in mean HDL-C level was 19% in the OCALIVA 10 mg arm, 12% in the OCALIVA titration arm, and 2% in the placebo arm. Nine patients in the OCALIVA 10 mg arm, 6 patients in the OCALIVA titration arm, versus 3 patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL.

Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hepatic Decompensation and Failure in PBC Patients with Cirrhosis *[see Warnings and Precautions (5.1)]*
- Severe Pruritus *[see Warnings and Precautions (5.2)]*
- Reduction in HDL-C *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 432 patients with PBC were studied in three double-blind, placebo-controlled clinical trials. Of these patients, 290 were treated with OCALIVA for at least 6 months, 232 were treated for at least 12 months, and 70 were treated for at least 2 years. There were 131 patients who received OCALIVA 10 mg once daily and 70 who received OCALIVA 5 mg once daily.

In Trial 1, 216 patients were randomized (1:1:1) to receive either:

- OCALIVA 10 mg once daily for the entire 12 months of the trial (n=73)
- OCALIVA titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months, in patients who were tolerating OCALIVA, but had ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction) (n=70); or
- placebo (n=73).

During the trial, OCALIVA or placebo was administered in combination with UDCA in 93% of patients and as monotherapy in 7% of patients who were unable to tolerate UDCA. The overall discontinuation

rate was 12% in the OCALIVA 10 mg arm, 10% in the OCALIVA titration arm, and 4% in the placebo arm.

The recommended starting dosage of OCALIVA is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response *[see Dosage and Administration (2.2)]*. Initiation of therapy with OCALIVA 10 mg once daily is not recommended due to an increased risk of pruritus.

The most common adverse reactions in Trial 1 occurring in at least 5% of patients in either OCALIVA treatment arm and at an incidence at least 1% higher than the placebo treatment arm are shown in Table 1.

Table 1: Most Common Adverse Reactions in Adult Patients with PBC in Trial 1 by Treatment Arm with or without UDCA[a]

Adverse Reaction[b]	OCALIVA 10 mg N=73 %	OCALIVA Titration[c] N=70 %	Placebo N=73 %
Pruritus[d]	70	56	38
Fatigue[e]	25	19	15
Abdominal pain and discomfort[f]	10	19	14
Rash[g]	10	7	8
Arthralgia	10	6	4
Oropharyngeal pain	8	7	1
Dizziness[h]	7	7	5
Constipation	7	7	5
Peripheral Edema	7	3	3
Palpitations	7	3	1
Pyrexia	7	0	1
Thyroid function abnormality[i]	4	6	3
Eczema	3	6	0

[a] In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

[b] Occurring in greater than or equal to 5% of patients in either OCALIVA treatment arm and at an incidence greater than or equal to1% higher than in the placebo treatment arm.

[c] Patients randomized to OCALIVA titration received OCALIVA 5 mg once daily for the initial 6-month period. At Month 6, patients who were tolerating OCALIVA, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.

[d] Includes skin eruptions, prurigo, pruritus, pruritus generalized, eye pruritus, ear pruritus, anal pruritus, vulvovaginal pruritus, rash pruritic.

[e] Includes fatigue, tiredness, asthenia.

[f] Includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, abdominal tenderness, gastrointestinal pain.

[g] Includes urticaria, rash, rash macular, rash papular, rash maculo-papular, heat rash, urticaria cholinergic.

[h] Includes dizziness, syncope, presyncope.
[i] Includes thyroxine free decreased, blood thyroid stimulating hormone increased, hypothyroidism.

Hepatic Adverse Reactions

In Trial 1, the following serious or otherwise clinically significant hepatic adverse reactions were reported at the recommended dosage of OCALIVA: one patient in the OCALIVA 10 mg treatment arm experienced ascites; one patient in the OCALIVA titration treatment arm experienced two episodes of ascites and four episodes of hepatic encephalopathy; one patient in the placebo treatment arm experienced variceal bleeding.

Pruritus

Approximately 60% of patients had a history of pruritus upon enrollment in Trial 1. Treatment-emergent pruritus, including all the terms described in Table 1, generally started within the first month following the initiation of treatment with OCALIVA.

The incidence of pruritus was higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 70% and 56%, respectively. Discontinuation rates due to pruritus were also higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 10% and 1%, respectively.

The number of patients with pruritus who required an intervention (e.g., dosage adjustment, treatment interruption, or initiation of bile acid binding resin or antihistamine) was 30 of 51 patients (59%) in the OCALIVA 10 mg arm, 24 of 39 patients (62%) in the OCALIVA titration arm, and 14 of 28 patients (50%) in the placebo arm.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of OCALIVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure, particularly in PBC patients who have progressive liver disease.

Hepatobiliary Disorders: liver failure, new onset cirrhosis, increased direct and total bilirubin, new or worsening of jaundice *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Bile Acid Binding Resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCALIVA. If taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible *[see Dosage and Administration (2.5)]*.

7.2 Warfarin

The International Normalized Ratio (INR) decreased following coadministration of warfarin and OCALIVA *[see Clinical Pharmacology (12.3)]*. Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin.

7.3 CYP1A2 Substrates with Narrow Therapeutic Index

Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates *[see Clinical Pharmacology (12.3)]*. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline and tizanidine) is recommended when co-administered with OCALIVA.

7.4 Inhibitors of Bile Salt Efflux Pump

Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine *[see Clinical Pharmacology (12.3)]*. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts including taurine conjugate of obeticholic acid in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitor serum transaminases and bilirubin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available human data on the use of obeticholic acid during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13-times and 6-times human exposures, respectively, at the maximum recommended human dose (MRHD) of 10 mg *[see Data below]*.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, obeticholic acid was administered orally during the period of organogenesis at doses of 5, 25, and 75 mg/kg/day. At 25 mg/kg/day (a dose that produced systemic exposures approximately 13-times those in humans at the MRHD of 10 mg), there was no maternal or developmental toxicity. At 75 mg/kg/day (approximately 40-times the human exposure at the MRHD), decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses were observed. In maternal animals, mortality, fetal loss, decreased body weight and food consumption as well as decreased body weight gain were observed at 75 mg/kg/day. Thus, the developmental toxicity observed at this dose may be secondary to maternal toxicity. In rabbits, obeticholic acid was administered orally during the period of organogenesis at doses of 3, 9, and 20 mg/kg/day. Obeticholic

acid administered at doses up to 20 mg/kg/day (approximately 6-times the human exposure at the MRHD) was not teratogenic and did not produce any evidence of fetal harm.

In a pre- and post-natal development study, administration of obeticholic acid in rats during organogenesis through lactation at doses of 5, 25, and 40 mg/kg/day did not produce effects on pregnancy, parturition, or postnatal development at any dose (the 40 mg/kg/day dose is approximately 21-times the human exposure at the MRHD).

Obeticholic acid exposure margins were calculated using systemic exposure (AUC) values of obeticholic acid plus obeticholic acid's active metabolite conjugates (tauro-obeticholic acid and glyco-obeticholic acid) in animals (at the indicated doses) and in humans at the MRHD of 10 mg.

8.2 Lactation

Risk Summary

There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OCALIVA and any potential adverse effects on the breastfed infant from OCALIVA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of OCALIVA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 201 patients in clinical trials of OCALIVA who received the recommended dosage (5 mg or 10 mg once daily), 41 (20%) were 65 years of age and older, while 9 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and patients less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in PBC patients with cirrhosis, either compensated or decompensated *[see Warnings and Precautions (5.1)]*. OCALIVA is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C), in those with a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) *[see Contraindications (4)]*.

In PBC clinical trials, a dose-response relationship was observed for the occurrence of hepatic adverse reactions with OCALIVA *[see Warnings and Precautions (5.1)]*.

Plasma exposure to obeticholic acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

Routinely monitor patients for progression of PBC with laboratory and clinical assessments. Closely monitor patients with compensated cirrhosis, concomitant hepatic disease, and/or severe intercurrent illness for new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) or increases above the upper limit of normal in total bilirubin, direct bilirubin, or

prothrombin time to determine whether drug discontinuation is needed. Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment. Interrupt treatment during severe intercurrent illness *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

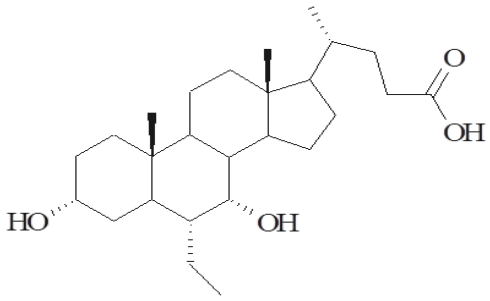
In the clinical trials, PBC patients who received OCALIVA 25 mg once daily (2.5-times the highest recommended dosage) or 50 mg once daily (5-times the highest recommended dosage) experienced a dose-dependent increase in the incidence of hepatic adverse reactions, including elevations in liver biochemical tests, ascites, jaundice, portal hypertension, and primary biliary cholangitis flares.

Serious hepatic adverse reactions have been reported postmarketing in PBC patients with decompensated cirrhosis when OCALIVA was dosed more frequently than the recommended dosage; these adverse reactions were also reported in some patients who received the recommended dosage *[see Contraindications (4), Warnings and Precautions (5.1)]*.

In the case of overdosage, patients should be carefully observed, and supportive care administered, as appropriate.

11 DESCRIPTION

OCALIVA is a farnesoid X receptor (FXR) agonist. Chemically, obeticholic acid is 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid. It is a white to off-white powder. It is soluble in methanol, acetone and ethyl acetate. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH. Its chemical formula is $C_{26}H_{44}O_4$, the molecular weight is 420.63 g/mol, and the chemical structure is:



OCALIVA tablets are supplied in 5 mg and 10 mg strengths for oral administration. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating is Opadry II (Yellow) containing polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol (polyethylene glycol 3350), talc, and iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Obeticholic acid is an agonist for FXR, a nuclear receptor expressed in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing *de novo* synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.

12.2 Pharmacodynamics

Dose Titration

In Trial 1, ALP reduction was observed to plateau at approximately 3 months in most patients treated with OCALIVA 5 mg once daily. Increasing the dosage of OCALIVA to 10 mg once daily based on tolerability and response provided additional reduction in ALP in the majority of patients *[see Dosage and Administration (2.2), Clinical Studies (14)]*.

Pharmacodynamic Markers

In Trial 1, administration of OCALIVA 10 mg once daily was associated with a 173% increase in concentrations of FGF-19, an FXR-inducible enterokine involved in bile acid homeostasis, from baseline to Month 12. Concentrations of cholic acid and chenodeoxycholic acid were reduced 2.7 micromolar and 1.4 micromolar, respectively, from baseline to Month 12. The clinical relevance of these findings is unknown.

Cardiac Electrophysiology

At a dose of 10-times the maximum recommended dose, OCALIVA does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Following multiple oral doses of OCALIVA 10 mg once daily, peak plasma concentrations (C_{max}) of obeticholic acid occurred at a median time (T_{max}) of approximately 1.5 hours. The median T_{max} for both the glyco- and tauro-conjugates of obeticholic acid was 10 hours. Coadministration with food did not alter the extent of absorption of obeticholic acid *[see Dosage and Administration (2.5)]*.

Following multiple-dose administration of OCALIVA 5, 10, and 25 mg once daily (2.5-times the highest recommend dosage) for 14 days, systemic exposures of obeticholic acid increased dose proportionally. Exposures to glyco-obeticholic acid and tauro-obeticholic acid, and total obeticholic acid (the sum of obeticholic acid and its two active conjugates) increased more than proportionally with dose. The steady-state systemic exposure (AUC_{0-24h}) achieved on Day 14 of total obeticholic acid was 4.2-, 6.6-, and 7.8- fold the systemic exposure (AUC_{0-24h}) achieved on Day 1 after 5, 10, and 25 mg once daily dosing, respectively.

Distribution

Human plasma protein binding of obeticholic acid and its conjugates is greater than 99%. The volume of distribution of obeticholic acid is 618 L. The volumes of distribution of glyco- and tauro-obeticholic acid have not been determined.

Elimination

Metabolism

Obeticholic acid is conjugated with glycine or taurine in the liver and secreted into bile. These glycine and taurine conjugates of obeticholic acid are absorbed in the small intestine leading to enterohepatic recirculation. The conjugates can be deconjugated in the ileum and colon by intestinal microbiota, leading to the conversion to obeticholic acid that can be reabsorbed or excreted in feces, the principal route of elimination.

After daily administration of obeticholic acid, there was accumulation of the glycine and taurine conjugates of obeticholic acid, which have *in vitro* pharmacological activities similar to the parent drug, obeticholic acid. The metabolite-to-parent ratios of the glycine and taurine conjugates of obeticholic acid were 13.8 and 12.3 respectively, after daily administration. An additional third obeticholic acid metabolite, 3-glucuronide, was formed but was considered to have minimal pharmacologic activity.

Excretion

After administration of radiolabeled obeticholic acid, about 87% of the dose was excreted in feces through biliary secretion. Less than 3% of the dose was excreted in the urine with no detection of obeticholic acid.

Specific Populations

Body weight, Age, Sex Race/Ethnicity: Based on population pharmacokinetic analysis, body weight was a significant predictor of obeticholic acid pharmacokinetics with lower obeticholic acid exposure expected with higher body weight. The body weight effect is not expected to cause a meaningful impact on efficacy. The pharmacokinetics of obeticholic acid would not be expected to be altered based on age, sex, or race/ethnicity.

Renal Impairment: In a single-dose pharmacokinetic study using 25 mg of obeticholic acid (2.5-times the highest recommended dosage), mean AUC of total obeticholic acid was increased by approximately 1.4- to 1.6-fold in subjects with mild (eGFR 60 to 89 mL/min/1.73 m^2 using the modification of diet in renal disease [MDRD] equation), moderate (eGFR 30 to 59 mL/min/1.73 m^2 by MDRD), and severe (eGFR 15 to 29 mL/min/1.73 m^2 by MDRD) renal impairment compared to subjects with normal renal function. This increase is not considered to be clinically meaningful.

Hepatic Impairment: Obeticholic acid is metabolized in the liver. In subjects with mild, moderate, and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), the mean AUC of total obeticholic acid increased 1.1-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg OCALIVA *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Effect of Obeticholic Acid on Other Drugs

Based on *in vitro* studies, obeticholic acid can inhibit CYP3A4. However, an *in vivo* study indicated no inhibition of CYP3A4 by obeticholic acid at the recommended dose of OCALIVA. Obeticholic acid is not expected to inhibit CYPs 2B6, 2C8, 2C9, 2C19, and 2D6, or induce CYPs 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4 at the recommended dose of OCALIVA. Down-regulation of mRNA was observed in a concentration-dependent fashion for CYP1A2 and CYP3A4 by obeticholic acid and its glycine and taurine conjugates.

In vitro studies suggest that there is potential for obeticholic acid and its glycine and taurine conjugates to inhibit OATP1B1 and OATP1B3 (the clinical significance of which is unknown), but not P-gp, BCRP, OAT1, OAT3, OCT2, and MATE transporters, at the recommended dose of OCALIVA.

In vitro studies showed that obeticholic acid and its glycine and taurine conjugates inhibit BSEP in a dose dependent manner. However, an *in vivo* drug interaction due to inhibition of BSEP in patients using the recommended dosage regimen appears unlikely.

Induction of BSEP can occur by FXR activation by obeticholic acid and its conjugates, which are FXR agonists.

Warfarin: Concomitant administration of 25 mg warfarin as a single dose with OCALIVA 10 mg once daily resulted in 13% increase in systemic exposure to S-warfarin and 11% decrease in maximum INR *[see Drug Interactions (7.2)]*.

Caffeine (CYP1A2 substrate): Concomitant administration of 200 mg caffeine as a single dose with OCALIVA 10 mg once daily resulted in a 42% increase in plasma AUC and 6% increase in C_{max} of caffeine *[see Drug Interactions (7.3)]*.

Omeprazole (CYP2C19 substrate): Concomitant administration of 20 mg omeprazole as a single dose with OCALIVA 10 mg once daily resulted in a 32% increase in AUC and a 33% increase in C_{max} of omeprazole. The clinical significance is unknown.

No clinically relevant interactions were seen when the following drugs were administered as single doses concomitantly with OCALIVA 10 mg once daily:

Midazolam 2 mg (CYP3A4 substrate): 2% increase in AUC and C_{max} of midazolam.

Dextromethorphan 30 mg (CYP2D6 substrate): 11% decrease in AUC and 12% decrease in C_{max} of dextromethorphan.

Digoxin 0.25 mg (P-gp substrate): 1% increase in AUC and 3% decrease in C_{max} of digoxin.

Rosuvastatin 20 mg (BCRP, OATP1B1, OATP1B3 substrate): 22% increase in AUC and a 27% increase in C_{max} of rosuvastatin.

Effect of Other Drugs on Obeticholic Acid

In vitro data suggest that obeticholic acid is not metabolized to any significant extent by CYP450 enzymes.

Proton Pump Inhibitors (omeprazole): Concomitant administration of 20 mg omeprazole once daily with OCALIVA 10 mg once daily resulted in a less than 1.2-fold increase in obeticholic acid plasma

exposure. This increase is not expected to be clinically meaningful. Concomitant administration of 40 mg omeprazole once daily with OCALIVA 10 mg once daily was not studied.

BSEP inhibitors: In vitro data indicate that tauro-obeticholic acid is a substrate of BSEP *[see Drug Interactions (7.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of obeticholic acid was assessed in carcinogenicity studies of up to 2 years in duration in mice and rats. In mice, there were no drug-related neoplastic findings at doses up to 25 mg/kg/day obeticholic acid, a dose that produced systemic exposures approximately 12-times those in humans at the MRHD of 10 mg. In rats, obeticholic acid was administered at doses of 2, 7, and 20 mg/kg/day. At 20 mg/kg/day (approximately 12-times the human exposure at the MRHD), obeticholic acid caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats.

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

Obeticholic acid, administered at oral doses of 5, 25, and 50 mg/kg/day to male rats for 28 days before mating and throughout the mating period, and to female rats from 14 days before mating through mating and until gestation day 7, did not alter male or female fertility or early embryonic development at any dose (the 50 mg/kg/day dose is approximately 13-times the human exposure at the MRHD).

14 CLINICAL STUDIES

The recommended starting dosage of OCALIVA is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response *[see Dosage and Administration (2.2)]*. Initiation of therapy with a starting dosage OCALIVA 10 mg once daily is not recommended due to an increased risk of pruritus *[see Adverse Reactions (6.1)]*.

Trial 1 was a randomized, double-blind, placebo-controlled, 12-month clinical trial which evaluated the safety and efficacy of OCALIVA in 216 patients with PBC who were taking UDCA for at least 12 months (on a stable dosage for at least 3 months), or who were unable to tolerate UDCA and did not receive UDCA for at least 3 months. Patients were included in the trial if the ALP was 1.67-times upper limit of normal (ULN) or greater and/or if total bilirubin was greater than 1-times ULN but less than 2-times ULN. Patients were excluded from the trial if they had other liver disease, presence of clinically significant hepatic decompensation events (i.e., portal hypertension and its complications, cirrhosis with

complications, or hepato-renal syndrome), severe pruritus, or Model for End Stage Liver Disease (MELD) score of 15 or greater.

Patients were randomized (1:1:1) to receive either OCALIVA 10 mg once daily for the entire 12 months of the trial, (n=73); OCALIVA titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months if the patient was tolerating OCALIVA but had ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction) (n=70); or placebo (n=73). OCALIVA or placebo was administered in combination with UDCA in 93% of patients during the trial and as monotherapy in 7% of patients who were unable to tolerate UDCA.

The primary endpoint was a responder analysis at Month 12, where response was defined as a composite of three criteria: ALP less than 1.67-times the ULN, total bilirubin less than or equal to ULN, and an ALP decrease of at least 15%. The ULN for ALP was defined as 118 U/L for females and 124 U/L for males. The ULN for total bilirubin was defined as 1.1 mg/dL for females and 1.5 mg/dL for males.

The study population was 91% female and 94% white. The mean age was 56 years (range 29 to 86 years). The mean baseline ALP concentration was 323.2 U/L, corresponding to 2.74-times ULN. Approximately 29% of the patients had ALP concentration levels greater than 3-times the ULN. The mean baseline total bilirubin concentration was 0.65 mg/dL and was less than or equal to the ULN in 92% of the enrolled patients. Distribution of patients by Rotterdam disease stage criteria at baseline is shown in Table 2. Cirrhosis was present at baseline in 4 patients (5%) in the OCALIVA 10 mg arm, 7 patients (10%) in the OCALIVA titration arm, and 9 patients (12%) in the placebo arm.

Table 2: Rotterdam Disease Stage Criteria at Baseline in Trial 1 by Treatment Arm with or without UDCA[a]

Disease Stage[b]	OCALIVA 10 mg (N=73)	OCALIVA Titration (N=70)	Placebo (N=73)
Early, n (%)	66 (90)	64 (91)	65 (89)
Moderately Advanced, n (%)	7 (10)	6 (9)	8 (11)
Advanced, n (%)	0 (0)	0 (0)	0 (0)

Percentages are based on non-missing values for each time point.

[a] In the trial, there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

[b] Early: normal total bilirubin and normal albumin (values less than or equal to ULN and greater than or equal to the lower limit of normal (LLN), respectively), Moderately advanced: abnormal total bilirubin or abnormal albumin, Advanced: abnormal total bilirubin and abnormal albumin. Total bilirubin ULN: 1.1 mg/dL (females) and 1.5 mg/dL (males). Albumin LLN: 35 g/L (females and males).

Table 3 shows the percentage of patients by treatment arm in Trial 1 who achieved a response to the primary composite endpoint at Month 12, and to the individual components of the primary endpoint (i.e., ALP less than 1.67-times the ULN, total bilirubin less than or equal to ULN, and an ALP decrease of at least 15%). A total of 33 patients in the OCALIVA titration arm, who did not achieve a response at 6 months and tolerated OCALIVA, had their dosage increased from 5 mg once daily to 10 mg once daily. Of these 33 patients, 13 (39%) achieved the primary composite endpoint at 12 months.

Table 3: Percentage of Adult Patients with PBC Achieving the Primary Composite Endpoint at Month 12 in Trial 1 by Treatment Arm with or without UDCA[a]

	OCALIVA 10 mg (N=73)	OCALIVA Titration[b] (N=70)	Placebo (N=73)
Primary Composite Endpoint[c]			
Responder rate, (%)[d] [95% CI]	48 [36, 60]	46 [34, 58]	10 [4, 19]
Components of Primary Endpoint[e]			
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[f], n (%)	60 (82)	62 (89)	57 (78)

[a] In the trial, there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

[b] Patients randomized to OCALIVA titration received OCALIVA 5 mg for the initial 6-month period. At Month 6, patients who were tolerating OCALIVA, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.

[c] Percentage of patients achieving a response, defined as an ALP less than 1.67-times the ULN, total bilirubin less than or equal to the ULN, and an ALP decrease of at least 15%. Missing values were considered a non-response. The exact test was used to calculate the 95% CIs.

[d] $p<0.0001$ for OCALIVA titration and OCALIVA 10 mg arms versus placebo. P-values are obtained using the Cochran–Mantel–Haenszel General Association test stratified by intolerance to UDCA and pretreatment ALP greater than 3-times ULN and/or AST greater than 2-times ULN and/or total bilirubin greater than ULN.

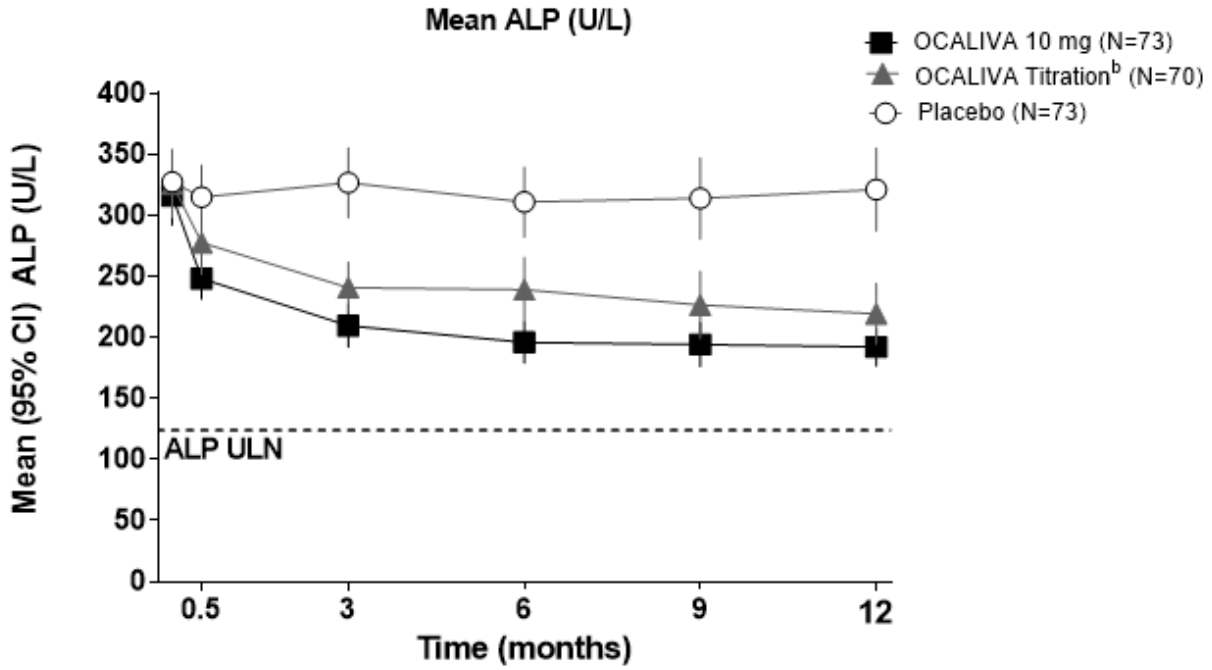
[e] Response rates were calculated based on the observed case analysis (i.e., [n=observed responder]/[N=ITT population]); percentage of patients with Month 12 values are 86%, 91%, and 96% for the OCALIVA 10 mg, OCALIVA titration and placebo arms, respectively.

[f] The mean baseline total bilirubin value was 0.65 mg/dL, and was less than or equal to the ULN in 92% of the enrolled patients.

Mean Reduction in ALP

Figure 1 shows the mean reductions in ALP in OCALIVA-treated patients compared to placebo. Reductions were observed as early as Week 2, plateaued by Month 3 and were maintained through Month 12 for patients who were maintained on the same dosage throughout 12 months. Although Trial 1 studied titration at 6 months, these data are supportive of titration of OCALIVA after 3 months *[see Dosage and Administration (2.2)]*. For patients in the OCALIVA titration arm whose OCALIVA dosage was increased from 5 mg once daily to 10 mg once daily, additional reductions in ALP were observed at Month 12 in the majority of patients *[see Clinical Pharmacology (12.2)]*.

Figure 1: Mean ALP over 12 Months in Trial 1 by Treatment Arm with or without UDCA[a]



[a] In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

[b] Patients randomized to OCALIVA titration received OCALIVA 5 mg once daily for the initial 6-month period. At Month 6, patients who were tolerating OCALIVA, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.

Mean Reduction in GGT

The mean (95% CI) reduction in gamma-glutamyl transferase (GGT) was 178 (137, 219) U/L in the OCALIVA 10 mg arm, 138 (102, 174) U/L in the OCALIVA titration arm, and 8 (-32, 48) U/L in the placebo arm.

OCALIVA Monotherapy

Fifty-one PBC patients with baseline ALP 1.67-times ULN or greater and/or total bilirubin greater than ULN were evaluated for a biochemical response to OCALIVA as monotherapy (24 patients received OCALIVA 10 mg once daily and 27 patients received placebo) in a pooled analysis of data from Trial 1 and from a randomized, double-blind, placebo-controlled, 3-month clinical trial. At Month 3, 9 (38%) OCALIVA-treated patients achieved a response to the composite endpoint, compared to 1 (4%) placebo-treated patient. The mean (95% CI) reduction in ALP in OCALIVA-treated patients was 246 (165, 327) U/L compared to an increase of 17 (-7, 42) U/L in the placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

OCALIVA tablets are packaged in a 40 mL high density polyethylene bottle closed with a 33 mm polypropylene child resistant cap containing an induction seal. Each bottle contains 30 tablets.

5 mg Tablets

OCALIVA tablets are available as off-white to yellow, round tablets debossed with INT on one side and 5 on the other side. Each tablet contains 5 mg of obeticholic acid.

- NDC 69516-005-30 5 mg tablets in a bottle (30 count)

10 mg Tablets

OCALIVA tablets are available as off-white to yellow, triangular tablets debossed with INT on one side and 10 on the other side. Each tablet contains 10 mg of obeticholic acid.

- NDC 69516-010-30 10 mg tablets in a bottle (30 count)

Storage and Handling

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatic Decompensation and Failure in PBC Patients with Cirrhosis

- Instruct patients and caregivers to immediately contact their healthcare provider if they experience:
  - Symptoms of disease progression or worsening liver function, such as ascites, jaundice, variceal bleeding, or hepatic encephalopathy.
  - Symptoms of complete biliary obstruction *[see Contraindications (4), Warnings and Precautions (5.1)]*.
  - Severe or persistent non-specific signs and symptoms of impaired health:
    - nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite, or dehydration.
- Inform patients that they will need to undergo laboratory testing periodically while on OCALIVA treatment to assess liver function.

Severe Pruritus

- Advise patients to contact their healthcare provider if they experience new onset or worsening severe pruritus *[see Warnings and Precautions (5.2)]*.

Reduction in HDL-C

- Advise patients that they may need to undergo laboratory testing to check for changes in lipid levels while on treatment with OCALIVA *[see Warnings and Precautions (5.3)]*.

Administration

Advise patients to take:

- OCALIVA with or without food.

- OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible *[see Drug Interactions (7.1)]*.

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Distributed by:

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