FDA Briefing Document

NDA# 207999

Drug name: Obeticholic Acid

Applicant: Intercept Pharmaceuticals, Inc.

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting

09/13/2024

Division of Hepatology and Nutrition/Office of Inflammation and Immunology

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought New Drug Application (NDA) 207999 for OCALIVA (Obeticholic acid, OCA), a farnesoid X receptor agonist, to this Advisory Committee in order to gain the Committee's perspective on whether Trial 747-302 and observational (noninterventional) study 747-405 fulfill the requirement that a drug approved under accelerated approval regulations, 21 CFR 314.510, demonstrates clinical benefit. Trial 747-302 and observational study 747-405 were intended to demonstrate clinical benefit of OCA for the indication "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." The background package may not include all issues relevant to the final regulatory decision and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final decision on the application until input from the Advisory Committee process has been considered and all reviews have been finalized. FDA's action on the application will be based upon our detailed and comprehensive review and thorough consideration of the input we receive from the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
AE	adverse event
AESI	adverse event of special interest
AMA	anti-mitochondrial antibody
AIH	autoimmune hepatitis
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BD	Briefing Document
BSEP	bile salt export pump
CDCA	chenodeoxycholic acid
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CP	Child Turcotte Pugh Score
CRC	clean room committee
CSR	clinical study report
DHN	Division of Hepatology and Nutrition
DILI	drug-induced liver injury
DMC	data monitoring committee
EOS	end of study
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FXR	farnesoid X receptor
HE	hepatic Encephalopathy
HI	hepatic impairment
HLT	high-level term
HOC	hepatic outcomes committee
HR	hazard ratio
HSAC	hepatic safety adjudication committee
IA	integrated assessment
ICD-10	International Classification of Disease, 10th Revision
IR	incidence rate

ITT	intention to treat
kPa	kilopascal
LT	liver transplant
MELD	Model for End Stage Liver Disease
mITT	modified intention to treat
NASH	nonalcoholic steatohepatitis
NDA	new drug application
OCA	obeticholic acid (OCALIVA)
OPTN	Organ Procurement and Transplantation Network
OSI	Office of Scientific Investigations
PBC	primary biliary cholangitis
PD	pharmacodynamic
PK	pharmacokinetic
PMN	polymorph leukocyte
PMR	postmarketing requirement
PT	preferred term
PY	patient-year
QBA	quantitative bias analysis
RLSE	reasonably likely surrogate endpoint
RWE	real-world evidence
SAE	severe adverse event
SAP	statistical analysis plan
SBP	spontaneous bacterial peritonitis
SD	standard deviation
SMR	standardized morbidity ratio
SSDI	Social Security Death Index
TB	total bilirubin
TEAE	treatment-emergent adverse event
TEAESI	treatment-emergent adverse event of special interest
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
USPI	United States Prescribing Information

1 Introduction

1.1 Purpose/Objective of the AC Meeting

Executive Summary

The FDA is convening this AC meeting to discuss whether the data submitted by Intercept Pharma, Inc. (Applicant) verifies the clinical benefit of obeticholic acid (OCA, or Ocaliva®) for the treatment of primary biliary cholangitis in patients either intolerant to or unresponsive to ursodeoxycholic acid (UDCA). OCA is an FXR agonist that decreases bile acid synthesis and is hypothesized to attenuate PBC progression.

The AC will discuss whether the data submitted demonstrate clinical benefit and support a favorable benefit-risk assessment for the use of OCA for the treatment of PBC supporting traditional approval after the product received accelerated approval in 2016 based on the surrogate endpoint of alkaline phosphatase (ALP) and total bilirubin (TB). A clinical outcome is a characteristic or variable that directly measures a therapeutic effect of a drug, i.e., an effect on how a patient feels, functions, or survives. A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease.[1]

The Applicant submitted the results of the two postmarketing requirement (PMR) studies, randomized, double-blind, placebo-controlled Trials 747-302 (PMR 3057-1) and 747-401 (PMR 3057-1), and results from an observational cohort study (Study 747-405). Trial 747-302 was designed to evaluate the clinical benefit of OCA compared to placebo. The clinical outcomes evaluated included events of death, liver transplantation, and hospitalization due to hepatic decompensation events. Trial 747-401 was conducted to assess safety and PK/PD in subjects with Child-Pugh (CP) B and CP C. However, results from this trial are not discussed in detail in this document because this population is not eligible to receive OCA.

While the clinical trials were ongoing, the Agency identified reports submitted to the FDA Adverse Event Reporting System (FAERS) and published in the medical literature that described hepatotoxicity with Ocaliva use in patients with more advanced liver disease. Review of these cases led the Division of Hepatology and Nutrition to require Intercept to make significant labeling changes, including contraindicating the use of Ocaliva® in patients with PBC and decompensated cirrhosis, patients with a prior decompensation event, and patients with compensated cirrhosis with evidence of portal hypertension, and adding related information to the Boxed Warning and Warnings and Precautions sections of the labeling.

As a result of this regulatory action, Trial 747-401 was terminated because OCA was now contraindicated for the entire study population. Despite some study patients now being contraindicated for continuing in Trial 747-302, it reached study closure and achieved the target number of events based on an expanded definition of the primary composite endpoint.

Based on Trial 747-302, OCA failed to demonstrate efficacy on the expanded primary composite endpoint of liver transplantation, death, and liver-related outcomes in PBC subjects with chronic

[1] Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics Expedited Programs for Serious Conditions | Drugs and Biologics | FDA

disease. The Agency's analysis of data derived from Trial 747-302 also indicated unfavorable trends of OCA on liver transplantation and mortality in the ITT population and the USPI-labeled population.

Data submitted for observational study 747-405 were reviewed in accordance with FDA's guiding principles on reviewing the real-world evidence trials and the Applicant's request to substantiate its position that OCA offered clinical benefit (U.S. FDA 2023; July 2024). The Agency's current analysis of Study 747-405 concluded that OCA did not demonstrate clinical benefit compared to the PBC population not receiving OCA. The Agency seeks your input on the results of clinical trial and observational study, and the benefit-risk assessment of OCA for the proposed indication.

1.2 Context for Issues to Be Discussed at the AC

Accelerated Approval of OCA for PBC

Ocaliva is a FXR agonist that reduces liver bile acid synthesis and was approved under the accelerated pathway (Subpart H) on May 27, 2016. OCA was approved for treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Accelerated approval was supported by Trial 747-301, a randomized, double-blind, placebo-controlled clinical trial evaluating a surrogate endpoint that is considered reasonably likely to predict clinical benefit. The primary endpoint to gauge clinical effectiveness was a biochemical response at Month 12, where biochemical response is defined as: (1) alkaline phosphatase (ALP) <1.67× ULN; (2) reduction of ALP from baseline of at least 15%, and (3) normalization of total serum bilirubin (TB). Trial results demonstrated efficacy of OCA on this biochemical response compared to placebo, with 48% of subjects in the OCA 10 mg arm, 46% in the OCA titration arm, and 10% in the placebo arm meeting the primary endpoint.

OCA received accelerated approval for the entire spectrum of PBC severity (i.e., mild, moderate, and advanced disease), although ~93% of subjects enrolled in Trial 747-301 had early stage PBC[5]. PBC is a rare disease, affecting approximately 130,000 Americans (Lu 2018)[2] [3]. Applications can be approved through the accelerated approval pathway when there is substantial evidence of effectiveness on a surrogate endpoint (or intermediate clinical endpoint) that is assessed as reasonably likely to predict clinical benefit. Drugs approved using accelerated approval must subsequently conduct a clinical study or studies to verify clinical benefit.

PMRs were issued to verify the clinical benefit (PMR 3057-3) and to evaluate efficacy, PK, and safety in subjects with PBC and decompensated cirrhosis (CP-B and CP-C) (PMR 3057-1)[4].

Postmarketing Studies Verifying Clinical Benefit

The pivotal postmarketing trial, Trial 747-302, was a randomized, double-blind, placebo-controlled trial, conducted to meet the requirement for verifying clinical benefit of OCA. The trial enrolled noncirrhotic, CP A, or compensated; and CP B (decompensated) cirrhotic PBC subjects. Trial 747-302 was designed as an event-driven trial, i.e., the trial would be complete when the prespecified number of clinical outcome

[2] Lu M. Zhou Y, Haller I et al. Increasing prevalence of primary biliary cholangitis and reduced mortality with treatment. 2018;16(8):1342–1350.e12017.
[3] Primary Biliary Cholangitis: Patient Characteristics and the Health Care Economic Burden in the United States. Gastroenterol Hepatol (N Y). 2021;17(2 Suppl 3):9.
[4] Approval letter: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/207999Orig1s000ltr.pdf.

events was achieved. Trial 747-302 evaluated clinical outcome events including death, liver transplantation, and hepatic decompensation events leading to hospitalization (e.g., variceal hemorrhage, spontaneous bacterial peritonitis [SBP], hepatic encephalopathy [HE]), uncontrolled ascites, and need for paracentesis.

The Applicant also conducted a second PMR study, Trial 747-401. This was a 2-year trial of the safety, tolerability, and PK/PD in subjects with PBC who had decompensated cirrhosis (i.e., CP B and CP C cirrhosis).

Safety Concerns Leading to Two USPI Labeling Changes and Boxed Warnings: A brief overview of the regulatory history is provided below. For details refer to Sections 3.2, 4.2, and 4.3.

On February 1, 2018, the FDA added a Boxed Warning to the USPI, which highlighted the need to follow recommended dose reductions for PBC patients with decompensated cirrhosis, i.e., CP-B and CP-C cirrhosis. The labeling change was triggered by deaths and liver decompensation events that were reported to the FAERS after the approval of OCA in 2016. Most, but not all, cases were due to higher than recommended OCA dosing. Specifically, doses approved for noncirrhotic patients were administered to patients with PBC who had decompensated cirrhosis.

Up to May 2020, the Agency continued to receive reports of serious liver injury leading to liver decompensation or liver failure associated with use of OCA, despite appropriate dosing of patients with advanced cirrhosis. Consequently, the Agency opened a Newly Identified Safety Signal (NISS) for "liver disorder" to evaluate the hepatic safety adverse reactions reported to FAERS.

Based on the Agency's evaluation of cases reported to FAERS along with published reports of hepatoxicity related to OCA, the Agency required the Applicant to revise Ocaliva's labeling to add a contraindication for Ocaliva use patients with PBC and (1) decompensated cirrhosis; (2) a prior decompensation event; and (3) compensated cirrhosis who had evidence of portal hypertension. The risk for hepatoxicity in such patients with advanced liver disease was also added to the Boxed Warning and Warnings and Precautions sections of the Ocaliva® USPI. The revised labeling restrictions were disseminated in an FDA Drug Safety Communication on May 26, 2021 (FDA 2021).

After the USPI had been revised, Trial 747-401 was terminated in July 2021 because the entire study population was now contraindicated (i.e., patients with moderate (CP B cirrhosis) or severe hepatic impairment (CP C cirrhosis), or decompensated cirrhosis). Trial 747-401 will not be discussed here.

As a result of new contraindication, about 55% of subjects in Trial 747-302 were no longer eligible for OCA treatment. In this document, PBC subjects in Trial 747-302 who remained eligible for OCA are called the "USPI-Labeled Population." Subjects who were contraindicated according to the revised USPI are referred to as the "USPI-Contraindicated Population."

Consequences of May 2021 USPI Restrictions for Enrolled Population in Trial 747-302

Prior to the USPI restrictions, in December 2020, the DMC recommended no further enrollment in the postmarketing studies due to "no possibility of demonstrated clinical efficacy." The Applicant ceased enrolling subjects in Trial 747-302 and Trial 747-401.

Given the Applicant's challenges with retention and the Applicant's intention for early termination of Trial 747-302, FDA exercised regulatory flexibility and agreed with the Applicant to expand the definition

of the primary endpoint to accrue more events, and thus increase the power of the study compared to that using the previously specified primary endpoint for a given assumed treatment effect size (see Section 4.2). Prior to unblinding, the statistical analysis plan was also amended.

Study 747-405 Proposed to Demonstrate Clinical Effectiveness of OCA

In October 2021, the Applicant indicated it would submit real-world evidence (RWE) as part of its sNDA submission package to confirm clinical benefit. The Applicant explored several potential data sources to use as external controls to compare to subjects treated with Ocaliva. Alternatively, the Applicant considered conducting observational cohort studies. The Applicant considered using three databases: (1) Global PBC; (2) UK-PBC; and (3) Komodo. However, a Clean Room Committee (CRC) reported the following: (a) the Global PBC was inadequate for use due to an "insufficient sample size"; (b) the UK-PBC database was also inadequate for use due to data deficiencies, i.e., "obvious problems with the data." As a result, the Applicant conducted an observational cohort study using the Komodo database as Study 747-405 and submitted the results as part of this sNDA submission. Study 747-405 is an observational (retrospective) cohort study that included subjects between June 2016 and December 2021. It was designed to compare patients with PBC treated with Ocaliva or not, in terms of the risk of a composite endpoint with three components: (1) death; (2) liver transplantation; and (3) hepatic decompensation. In meetings of the Agency with the Applicant, the former indicated that the results of Study 747-405 may be supportive of the overall confirmation of clinical benefit in this application, but that Trial 747-302 was expected to serve as the primary study for the assessment of clinical benefit.

1.3 Brief Description of Issues for Discussion at the AC

Trial 747-302 Interpretation of Results

It is the Applicant's position that Trial 747-302 is uninterpretable and therefore could not serve as a basis to assess the efficacy or safety of OCA in the treatment of PBC (discussed in Section 4.2.5). However, following review of Trial 747-302, the Agency considers the results of Trial 747-302 to be interpretable, providing critical data to inform the safety and clinical effectiveness of OCA.

For Trial 747-302, the Agency conducted analyses for both safety and efficacy in the intention-to-treat (ITT) population, as prespecified by the Applicant, and in the USPI-labeled population. Of note, Trial 747-302 was not powered to demonstrate efficacy in the USPI-labeled population.

A core issue for discussion at this AC meeting is that Trial 747-302 failed to demonstrate a statistically significant benefit of OCA treatment on the prespecified primary endpoint analysis for the ITT population (hazard ratio of 0.84 [95% CI: 0.61, 1.16]), with the associated p-value of 0.304. While analyses of the USPI-labeled population are underpowered, the point estimate of the treatment effect on the primary endpoint in the USPI-labeled population was similar to that in the ITT population (hazard ratio of 0.88 [95% CI: 0.47, 1.65]). A hazard ratio less than 1 indicates a trend of benefit for OCA, and a hazard ratio greater than 1 indicates a trend of harm for OCA. Analyses of the key secondary endpoint evaluating liver transplant and death resulted in a hazard ratio of 1.18 (95% CI: 0.72, 1.93) for the ITT population and 4.77 (95% CI: 1.03, 22.09) for the USPI-labeled population (i.e., liver transplant/death results are in direction of harm).

In addition to safety events of death and liver transplants, safety analyses for Trial 747-302 are consistent with previously reported adverse events (AE) of DILI and pruritus (see Section 4.2.4).

Study 747-405 Interpretation of Results

The Agency has made a preliminary determination that Study 747-405 does not meet regulatory standards for an adequate and well-controlled clinical investigation. Study 747-405 combined administrative data (claims) with data from other sources and implemented a nonrandomized study with untreated control to assess PBC outcomes during treatment with OCA. The Agency's review determined that Study 747-405 used methods with unknown or uncertain reliability when (a) defining PBC with poor response to UDCA, (b) linking claims to external data sources, (c) identifying hepatic decompensation events, and (d) defining a follow-up period to adequately capture outcomes of interest. As described in the next paragraph, the Agency also questioned the Applicant's primary analysis method for Study 747-405, which failed to address potential informative censoring. After accounting for plausible impacts from erroneous data or improper analysis, the Agency finds that considerable doubt exists regarding the comparability of the OCA-treated and control conditions both at baseline and during follow-up.

The primary analysis of results from Study 747-405 as conducted by the Applicant used an as-treated (or while-on-treatment) strategy that estimated a hazard ratio associated with OCA of 0.37 with 95% CI (0.14, 0.75). However, the Agency identified several key limitations in the Applicant's as-treated analysis and considered the design of Study 747-405 as an insufficient research strategy to draw conclusions concerning the clinical effectiveness of OCA for traditional approval. Importantly, in the as-treated analysis, the mean follow-up time, the reasons for censoring, the proportions of patients censored, and the observed incidence rate of events after censoring, differed between patients treated with OCA and controls not treated with OCA. Collectively, this research strategy raises the possibility of informative censoring in the Applicant's analysis. (Informative censoring will be discussed in detail in this document.) In addition, the Agency conducted further statistical analyses that approximate an intent-to-treat strategy using a composite endpoint of death and liver transplantation. The FDA's ITT analyses yielded an estimated hazard ratio of 0.80 with 95% CI (0.45, 1.38) associated with OCA and do not demonstrate efficacy given that the confidence interval includes the null value of 1.

The limitations of Study 747-405 to meet the standards of an adequate and well-controlled investigation, and the limitations of the analyses conducted by both the Applicant and the Agency to estimate a clinically and statistically interpretable endpoint, suggest that Study 747-405 cannot serve as an adequate study to verify the clinical benefit.

2 Draft Points for Consideration

1. Consider whether the results from the randomized clinical outcomes trial (302) and observational study (405) confirm the clinical benefit of Ocaliva in preventing hepatic decompensation, liver transplant, and death in the treatment of primary biliary cholangitis.
2. If uncertainty remains regarding clinical benefit, consider whether additional observational data or another randomized clinical trial would be needed to confirm clinical benefit.
3. Consider whether the available evidence demonstrates that the clinical benefit of Ocaliva outweighs the risks for treatment of primary biliary cholangitis.

3 Background

3.1 Background of the Condition/Standard of Clinical Care

3.1.1 Background of Condition

Primary biliary cholangitis (PBC) is a rare, autoimmune, chronic cholestatic, and progressive liver disease that predominantly affects women. The ratio of females to males varies between 9:1 to 6:1 across various publications (Lv and Jia 2022). The etiology of PBC is multifactorial, potentially related to a combination of genetic risk and environmental triggers. The prevalence of disease is estimated between 19 and 402 cases per million (Younossi et al. 2019). The disease affects people of all races and ethnicities, globally (Cançado et al. 2022; Lv and Jia 2022).

Elevated ALT, ALP, and TB are diagnostic biomarkers for cholestatic liver disease, including PBC. The key diagnostic serologic signature is presence of antimitochondrial antibody (AMA), which is found in 95% of PBC patients. Histologically, PBC is characterized by chronic, nonsuppurative cholangitis with destruction of interlobular bile ducts. Over time, inflammation leads to ductopenia (loss of bile ducts), which causes progressive impairment of hepatic bile flow. Progressive destruction of intrahepatic bile ducts due to inflammation leads to increases in hepatocyte exposure to bile, cell injury, which ultimately may result in cirrhosis and liver failure, necessitating liver transplant or leading to death. The most frequent symptoms associated with PBC are fatigue (~78%) and pruritus (~70%). Other autoimmune diseases occur with increased frequency in association with PBC, including Sjögren syndrome; calcinosis, Raynaud, esophageal dysfunction, sclerodactyly, and telangiectasias (CREST); scleroderma (systemic sclerosis); and Raynaud disease.

The disease severity has been categorized as: noncirrhotic, compensated cirrhosis, and decompensated cirrhosis (de Franchis et al. 2022). The Rotterdam criteria[5] (Kuiper et al. 2009) use biochemical tests to categorize disease severity, which were used early in OCA drug development; however, these are not the primary criteria used to classify disease severity in this AC briefing document. Furthermore, there is no correlation between histological and biochemical criteria.

3.1.2 Drug Approved Under the Traditional Pathway

The current standard of care and first-line therapy for treatment of PBC is ursodeoxycholic acid (UDCA) which was approved by FDA on December 2, 1997. A multicenter randomized, double-blind placebo-controlled trial was conducted to assess the efficacy of UDCA. Treatment failure, the main efficacy endpoint measured in this study, was defined as death, need for liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites, or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin, and voluntary withdrawal. Using a definition of treatment failure that excluded a doubling of serum bilirubin and voluntary withdrawal, time to treatment failure was significantly delayed in the UDCA group.

The Division of Hepatology and Nutrition (DHN) has agreed with sponsors seeking accelerated approval for PBC based on a surrogate endpoint that is reasonably likely to predict clinical benefit (RLSE). DHN's

[5] Rotterdam criteria - 1) early stage with normal total bilirubin and normal albumin, 2) moderately advanced stage with either an elevated total bilirubin or low albumin or 3) advanced stage with both elevated total bilirubin and low albumin.

currently accepted RLSE is biochemical response, defined as ALP <1.67× ULN, reduction of ALP of at least 15%, and normalization of total bilirubin.

Published data for the RLSE are derived from multiple retrospective studies, in which patients with PBC were treated with long-term UDCA, including data analyzed by the Global PBC Study Group (Lammers et al. 2014). These analyses demonstrated that PBC patients who have a reduction in their serum alkaline phosphatase alone and/or in combination with TB, or ALP normalization, had improved survival. Hence, the PBC Study Group's findings suggest that treatment with UDCA improves liver-transplantation free survival.

Accelerated approval can provide patients with serious and life-threatening diseases access to new therapy sooner for conditions with an unmet need for treatment. Given that accelerated approval is based on the drug's effect on a surrogate endpoint, additional uncertainty is accepted as a tradeoff for providing earlier access to treatment. As a condition of the accelerated approval, sponsors are required to conduct postapproval studies to verify and describe the drug's clinical benefit.[6]

3.1.3 Drugs Approved Under Accelerated Approval Pathway (Subpart H)

The following three drugs have been approved under the accelerated approval pathway based on biochemical response, largely driven by reduction of ALP because TB was within the normal reference range in ~90 (87% to 92%) of the trial subjects, for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

4. Ocaliva (obeticholic acid, OCA) was approved on May 27, 2016.
5. Iqirvo (elafibranor), an agonist of peroxisome proliferator-activated receptor (PPAR) - alpha, -gamma, and -delta based on in vitro studies of PPAR agonism, was approved on June 10, 2024[7].
6. Levdelzi (seladelpar), a PPAR delta-agonist, was approved on August 14, 2024[8].

3.1.4 Off-Label Treatments

Currently, the U.S. and European liver society practice guidelines recommend the use of fibrates (including bezafibrates) as off-label alternatives for patients with PBC and inadequate response to UDCA.[9] [10]

3.1.5 Unmet Medical Need

Approximately 40% of patients with PBC have either an incomplete response or are unresponsive (including cirrhotic patients) to UDCA and about 5% are intolerant to UDCA. Therefore, treatment of PBC remains an unmet medical need. In addition, there are no FDA-approved therapeutics for the treatment of the symptoms of PBC, which is thus also an unmet medical need.

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[6] https://www.fda.gov/media/86377/download (Guidance Document - Expedited Programs for Serious Conditions | Drugs and Biologics)
[7] See the IQIRVO label at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218860s000lbl.pdf.
[8] See the LEVDELZI label at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217899s000lbl.pdf.
[9] Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2019;69(1):394-419.
[10] EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol*. 2017;67(1):145-172.

3.2 Regulatory History

3.2.1 Accelerated Approval of OCA

OCA was approved on May 27, 2016, under Subpart H (accelerated approval) for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. This approval was supported by the results from Trial 747-301 evaluating a primary endpoint of achieving biochemical response (i.e., ALP <1.67× ULN, 15% reduction in ALP from baseline, and normalization of bilirubin) at Month 12. Ninety-two percent (92%) of the subjects in Trial 747-301 had early stage PBC by the Rotterdam criteria[5]. Although the primary endpoint was prespecified as a reduction in both ALP and total bilirubin (TB), due to the nature of the enrolled population, the primary endpoint was primarily driven by reduction of serum ALP. The key adverse events identified included hepatotoxicity and new onset of worsening of pruritus, including severe pruritus that led to a requirement for the addition of antipruritic agents, decrease in dosing or frequency, drug holidays, or drug discontinuation.

Despite enrollment of subjects with early stage PBC in Trial 747-301, the labeled indication for OCA included treatment of PBC patients across the whole spectrum of disease, i.e., early stage, moderately advanced, and advanced stage (cirrhosis) disease. The rationale for this action in 2016 was based on the following: (1) PBC is a rare disease; (2) there were no effective treatments for patients with PBC who did not respond to UDCA or could not tolerate UDCA; and (3) based on the pathogenesis of the disease, the expectation was that intervention at any stage could provide a benefit to patients.

3.2.2 Postmarketing Requirement (PMR) Trial Development (747-302)

3.2.2.1 Endpoints

The Applicant and Agency agreed on two PMR trials, which included the confirmatory Trial 747-302 (phase 3b/4, randomized, double-blind, placebo controlled), which was initiated in December 2014 and was underway at the time of accelerated approval. This study was event driven, with the primary endpoint evaluating the time to first occurrence of any of the following outcomes: death, liver transplant, MELD ≥15, uncontrolled ascites, or hospitalization for a hepatic decompensation event.

3.2.2.2 Challenges in Recruitment and Retention in Trial 747-302

On August 11, 2019, the Applicant reported challenges in recruitment and retention with a rate of discontinuation reported at 51% with a high withdrawal rate in Trial 747-302. The Applicant proposed the option to compare subjects treated with Ocaliva in Trial 747-302 with untreated patients from an external control arm. The Agency communicated with the Applicant that the proposal to utilize an external control arm (historical control), would have similar limitations as any external control study would have, for example, potential lack of comparability with the treatment arm, the challenges in assessing prognostic factors that may confound comparisons, as well as the risk of selection bias. A historical comparator arm would also pose major limitations in assessing safety given the concerns for the potential hepatoxicity associated with OCA use in the PBC population (see Section 4.2).

3.2.2.3 DMC's Findings and Impact on Applicant's Postmarketing Study 747-302 and Study 747-401: Proposed Trial Modifications

In late 2020, the DMC convened to review unblinded Trial 747-302 data and concluded that Trial 747-302 was unlikely to provide evidence of efficacy for the enrolled population as an aggregate or in any subpopulation; that is, there was a high likelihood of futility. The DMC recommended no further enrollment in the Applicant's two PMR trials; of note, no safety concerns were reported by the DMC.

As Trial 747-401 enrolled Child-Pugh Class B cirrhosis (CP-B) and Child-Pugh Class C cirrhosis (CP-C) patient population, Trial 747-401 was terminated.

Following the DMCs findings, the Applicant proposed a revised strategy to verify the clinical benefit of Ocaliva with the following proposals: (1) not treat subjects with decompensated cirrhosis, i.e., CP-B and CP-C population (and terminate Trial 747-401); (2) convert the double-blind trial (747-302) to open-label treatment; (3) expand the primary endpoint clinical outcomes (Trial 747-302); and (4) use an external control arm (Trial 747-302). The Agency reiterated the importance of preserving the blinded, placebo-controlled, randomized design of Trial 747-302; and ultimately agreed with the Applicant's other proposals, specifically terminating Trial 747-401 (#1); restricting subject enrollment (#1) and participation (#1) as well as expanding the primary endpoint (#3; see Section 4.2.1.2 for expanded endpoints). With an expanded primary endpoint, Trial 747-302 reached trial closure, with the last subject completing on December 23, 2021.

3.2.3 Safety Issues Identified Following Approval

3.2.3.1 Medication Error Related to Dosing Patients with Advanced Cirrhosis

On September 12, 2017, a tracked safety issue (TSI 1834) was opened for Ocaliva based on a series of cases in which patients with decompensated cirrhosis (CP B and C) experienced hepatic decompensation when treated with doses higher than those labeled for patients with PBC and advanced cirrhosis. A Safety Labeling Change (SLC) notification letter was issued to the Applicant on September 17, 2017, which required the addition of a Boxed Warning and other labeling language highlighting the need for providers to adhere to recommended dose reductions for patients with advanced cirrhosis. Despite this USPI change, the Agency continued to receive safety reports, which raised concern that hepatoxicity was not limited to PBC patients with decompensated cirrhosis who received too high a dose. Specifically, these reports included patients with PBC and cirrhosis, compensated or decompensated, who were treated with the recommended labeled dose as adopted on February 1, 2018.

In May 2020, A Newly Identified Safety Signal (NISS)[11] was opened for *liver disorder*. A comprehensive review of FAERS and the medical literature identified 25 cases of serious liver injury leading to liver decompensation or liver failure associated with use of Ocaliva. All cases involved patients with PBC and cirrhosis (compensated or decompensated) taking Ocaliva at the recommended dosages prior to the reported liver-related adverse event(s).

On May 26, 2021, DHN issued an SLC Notification letter to the Applicant requiring the addition of a Contraindication Statement for Ocaliva use for (1) all patients with decompensated cirrhosis; (2) patients with a prior liver decompensation event even if resolved; and (3) patients with compensated cirrhosis who have clinical evidence of portal hypertension (e.g., esophageal varices). Related changes were also required for the Boxed Warning, Indications, Dosage and Administration, Warning and Precautions, Special Populations, and Patient Counseling Information sections of the Ocaliva USPI.

3.2.4 Regulatory History of Study 747-405

In December 2021 and January 2022, the Applicant discussed with the Agency its intent to submit nonrandomized evidence as part of its sNDA submission. On January 10, 2022, the FDA reiterated:

[11] The term "Newly Identified Safety Signal" replaced the earlier term "Tracked Safety Issue" that was in place in 2017 when the medication errors with OCA dosing were being reported.

> "We remind you that demonstration of efficacy should rely on results of the randomized controlled trial 747-302. You may submit RWE as supportive for the overall confirmation of clinical benefit, but data submitted from the results of trial 747-302 for Agency review will serve as the primary basis on which we will judge confirmation of clinical benefit."

The Applicant submitted the initial protocol of observational cohort study 747-405 in January 2022. The protocol described the primary composite endpoint, inclusion/exclusion criteria, and the study's intended trial emulation design. A protocol supplement submitted in April 2022 provided further information on the sources and processes for data collection and management. Between May and August 2022, the Study 747-405 Clean Room Committee (CRC) finalized design issues such as the choice of analysis window after treatment discontinuation, codes for the primary endpoint, and handling of outliers. The CRC is an external group charged with making decisions regarding important changes to the planned analysis or protocol.

In Meeting Minutes communicated to the Applicant on October 17, 2022, the FDA issued the following recommendations regarding the submission of real-world data:

> "To enable meaningful assessments for selection bias, information bias, confounding, and missing data, study reports should include:
> i. A rigorous and data-driven assessment for the potential of bias produced by differential application of criteria used to select OCA-treated and untreated patients for analysis.
> ii. A rigorous and data-driven assessment for the potential of bias produced by errors in measuring variables used to ascertain exposure to OCA, outcomes of clinical interest, and control factors for statistical analysis.
> iii. Transparent presentation of data quality as indicated by the completeness of information used to select patients for analysis, ascertain exposures to OCA, and determine outcomes of clinical interest."

Between July and November 2023, the Applicant and the Agency held multiple meetings to discuss the content and format for Study 747-405 data prior to submission. In November 2023, the Agency recommended that the analyses of the primary endpoint of the time to first event of hepatic decompensation, liver transplant, or death, consider all qualifying events and observation time regardless of censoring criteria:

> "Clarify whether any data, including the primary and secondary objectives, were collected for patients who met these censoring criteria. In particular, for patients who discontinued OCA (+90 days), initiated fenofibrate or bezafibrate, initiated OCA (for the non-OCA-treated patient – indices) or used an unapproved OCA dose (>10 mg once daily [QD]). If so, we recommend submitting these data, and conduct sensitivity and exploratory analyses to describe the safety outcomes experienced by these patients after they met these censoring criteria."

In response to this comment, the Applicant conducted the sensitivity analyses referred to as ITT-1 and ITT-2, which were included in the final submission (see Section 4.3, study 747-405).

3.3 Clinical Pharmacology Summary

3.3.1 Overview of Clinical Pharmacology

Clinical pharmacology information has been submitted to the original NDA and mostly reflected in the approved label.[12] In this supplement, plasma concentrations of OCA and its major metabolites were assessed in Trials 302 and 401. PK data from Trial 401 are not discussed in this document.

Mechanism of Action

OCA is a synthetic bile acid (6α-ethyl chenodeoxycholic acid) which has 100-fold more potent activity as an FXR agonist compared to the endogenous bile acid chenodeoxycholic acid (CDCA) (Zhang et al. 2017). In humans, OCA undergoes extensive metabolism and forms two major conjugates, glyco-OCA and tauro-OCA. In vitro glyco-OCA and tauro-OCA possess pharmacological activities similar to OCA.

FXR, a nuclear receptor is a key regulator of bile acid homeostasis (Sinal et al. 2000) and mediates its effect via inflammatory, fibrotic, and other metabolic pathways in the liver. FXR is expressed at high levels in liver, intestine, kidney, and adrenal glands. Ultimately FXR activation decreases de novo bile acid synthesis from cholesterol by inhibiting expression of cholesterol-7alpha-hydroxylase (CYP7A1), the rate-limiting enzyme for bile acid synthesis (Gupta et al. 2001).

FXR activation also induces bile salt export pump (BSEP) expression, the major transporter for bile acid secretion from hepatocytes into bile. In an in vitro study, OCA and its two major metabolites, glyco-OCA and tauro-OCA inhibited the transport of taurocholic acid via BSEP in a concentration-dependent manner. The inhibition of BSEP transport by OCA and its metabolites has the potential to lead to bile salt accumulation, including conjugates of OCA in the liver, leading to toxicity; however, the net effect on bile salt concentration in the liver may vary in different patient settings.

Pharmacokinetics

Based on substantially higher systemic exposure to glyco-OCA and tauro-OCA and their similar pharmacological activity, the systemic exposure was also analyzed as a sum of OCA, glycol-OCA and tauro-OCA, defined as total OCA.

Following multiple-OCA doses of 5, 10, and 25 mg once daily, systemic exposure of OCA increased in a dose-dependent manner while exposure to glyco-OCA and tauro-OCA increased more than proportionally with dose. Following once daily dosing of 5 mg, 10 mg, and 25 mg for 14 days, systemic exposure ($AUC_{0\text{-}24h}$) for total OCA was 4.2-, 6.6-, and 7.8-fold higher, respectively, compared to the systemic exposure on Day 1. At steady-state, systemic exposure ($AUC_{0\text{-}24}$) of the two major active conjugates, glyco-OCA and tauro-OCA, was 12- to 14-fold higher compared to unconjugated OCA. The systemic exposure of OCA, and its major conjugates, had moderate interindividual variability, with coefficients of variation (CV%) of 50% to 70% in healthy subjects.

In a study using radiolabeled OCA, OCA-related materials were detectable in the feces of healthy subjects for a prolonged period, such that following a single 25 mg OCA dose, radioactivity was detected in feces for 20 to 48 days.

Like endogenous bile acids, OCA and its respective conjugates are primarily excreted through bile and undergo enterohepatic circulation. OCA and its conjugates use similar molecular mechanisms for

[12] https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207999s008lbl.pdf.

uptake, conjugation, and biliary secretion as endogenous bile acids, e.g., tauro-OCA is a substrate of the BSEP localized on the canalicular membrane of hepatocytes, whereas glyco-OCA and tauro-OCA are substrates of the ileal bile acid transporter in the ileum. Glyco-OCA and tauro-OCA are also substrates for hepatic uptake transporters, sodium taurocholate cotransporting polypeptide (NTCP), organic anion transporting polypeptides (OATP)1B1, and OATP1B3.

Specific Populations

In subjects with mild to severe renal impairment (eGFR 15 to 90 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation), the total OCA exposure was 1.4- to 1.6-fold that in subjects with normal renal function. No dosage adjustment is recommended for patients with mild to severe renal impairment.

Hepatic impairment (HI)[13] significantly increases systemic exposure of total OCA. In a HI study conducted in subjects with non-PBC liver diseases (e.g., viral hepatitis) who also had mild, moderate, or severe HI as defined by CP-A, CP-B, and CP-C class, respectively, the mean AUC of total OCA increased by 1.1-, 4-, and 17-fold, respectively, as compared to subjects with normal hepatic function following a single dose of 10 mg OCA. No dosage adjustment is recommended for patients with mild hepatic impairment.

For patients with moderate and severe HI (CP-B and CP-C), based on the several fold (4- to 17-fold) increase in plasma exposure of total OCA and the signal of dose-response for pruritus in patients with PBC, an alternative dosing regimen of 5 mg QW (once weekly) was recommended as the starting dose using PK simulations to keep the systemic exposure similar to that in subjects with no or mild HI (CP-A). Furthermore, a dose increase to 5 mg twice weekly after the first 3 months of treatment and up to 10 mg twice weekly was recommended for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating OCALIVA. Refer to Table 2 for details. At the time of the original approval, OCA had not been studied in patients with PBC and moderate and severe HI.

QT Prolongation

After once daily dosing of 100 mg OCA for 5 days, there was no significant effect on the QT interval to any clinically relevant extent.

Drug Interactions

As for effects of other drugs on OCA, OCA is not metabolized by major CYP enzymes in vitro. Concomitant drugs that inhibit BSEP may affect the disposition of major metabolites of OCA. Therefore, concomitant use of OCA with inhibitors of BSEP transporter is not recommended.

Concomitant drugs that inhibit the ileal bile acid transporter can affect the PK of major metabolites of OCA.

Bile acid-binding resins may reduce the absorption, systemic exposure, and efficacy of OCA. OCA should be administered at least four hours before, or four hours after, taking bile acid sequestrants.

[13] CP-A is also called as mild hepatic impairment (HI) or compensated cirrhosis; CP-B is moderate HI or decompensated cirrhosis; and CP-C is severe HI or decompensated cirrhosis.

3.3.2 Study 747-302 Pharmacokinetics Results

Dosage Regimen

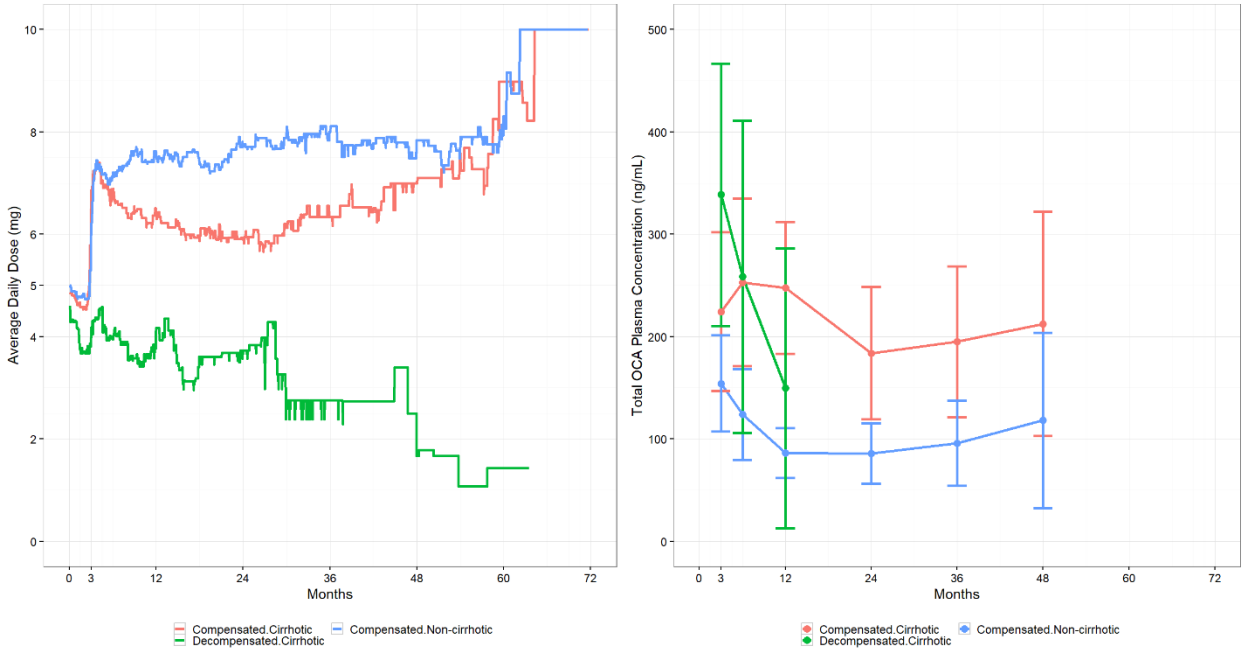
The PK of OCA in patients with PBC following administration of OCA was characterized in Trial 747-302 (the placebo-controlled outcomes trial discussed above). Initially, the 5 mg once daily dose increasing to 10 mg once daily after 3 months, if tolerated, was studied (Protocol Amendment 1.1, November 2015). Upon approval of Ocaliva (May 2016), alternative dosages for subjects with moderate to severe HI (CP B and C) were studied (see Table 2 in Section 4.2). Because subjects may titrate dose and dosing frequency up or down based on tolerability within the dosing regimen, other dosing frequencies, e.g., 5 mg three times a week and 10 mg every other day, were also noted in some patients. For noncirrhotic subjects and those with compensated cirrhosis at baseline, the mean daily dose was lower than 10 mg, the approved maximum daily dose, following dose escalation after treatment with 5 mg.

OCA Concentration in Plasma

The systemic exposure was higher in subjects with more advanced disease. The mean trough concentrations of total OCA were about two-fold higher in subjects with compensated cirrhosis at baseline than in noncirrhotic subjects, although the average daily dose was similar or lower (Figure 1). The difference in total OCA was due to conjugates of OCA, because the mean trough concentrations of OCA were similar in the two groups. The majority of subjects with compensated cirrhosis were classified into the USPI contraindicated population (Section 4.2.2.2, Table 5).

In a cross-study comparison, the mean trough concentrations for total OCA in USPI-labeled subjects were similar to those in subjects in Trial 301 at Month 12. In USPI-contraindicated subjects, the mean trough concentrations of total OCA were about two-fold higher compared to those in USPI-labeled subjects.

Figure 1. Average Daily OCA Dose and Mean Trough Concentrations of Total OCA by Cirrhosis Status at Baseline



Source: Reviewer's analysis based on adex.xpt and adpc.xpt for Trial 302.

In a subgroup of patients, serial PK samples were collected at Month 9. Although limited in sample size, the two subjects with moderate HI (CP-B) who received 10 mg twice a week had notably higher total OCA exposures (AUC_{0-6}, 4290 ng·h/mL; n=2) than subjects with mild HI (CP-A) who received 10 mg QD (AUC_{0-6}, 1310 ng·h/mL; n=3).

4 Ocaliva Clinical Development Program

4.1 Trial 747-301 (Trial to Support Accelerated Approval)

The results from Trial 747-301 were used to support the Accelerated Approval decision in 2016.

Study Design

Trial 747-301 included adult subjects with PBC who had ALP ≥1.67× ULN or TB >ULN but <2.0× ULN at baseline. Subjects were either taking UDCA for at least 12 months (with a stable dose for at least 3 months) prior to study start or unable to tolerate UDCA (i.e., no UDCA usage for at least 3 months) prior to study start. The study included a screening period of up to 8 weeks, a 12-month double-blinded, placebo-controlled treatment period, and an open-label extension period of up to 5 years.

Subjects were randomized in a 1:1:1 ratio to receive 10 mg OCA, 5 mg OCA once daily (QD) with the option to titrate up to 10 mg OCA at Month 6 (i.e., the OCA titration treatment arm), or matching placebo. The randomization was stratified by intolerance to UDCA (yes/no) and baseline biochemical values (yes/no, based on meeting any of ALP >3.0× ULN and/or AST >2.0× ULN and/or TB >ULN).

Summary of Efficacy

The primary endpoint for Trial 747-301 was a multicomponent endpoint in which a subject was designated as a biochemical responder if all three of the following conditions were met at Month 12: ALP <1.67× ULN, ALP reduction from baseline ≥15%, and TB ≤ULN.

The primary analysis set was a modified intent-to-treat (mITT) analysis set, which included all randomized subjects who received at least one dose of OCA. The primary analysis used a Cochran-Mantel-Haenszel (CMH) test adjusted for the randomization stratification variables. Subjects with missing data were considered nonresponders. To control the overall study-wise type I error rate when testing the two different dosing regimens, the primary endpoint was tested sequentially starting with the 10 mg OCA comparison to placebo. No other secondary endpoints were multiplicity adjusted.

A total of 217 subjects were randomized; 216 were administered at least one dose of study drug. Key baseline characteristics and subject disposition are in Table 21 and Table 20, respectively, in Section 8.1.

At Month 12, 46% to 47% of OCA-treated subjects and 10% of placebo-treated subjects achieved the primary efficacy endpoint of biochemical response at Month 12, and both OCA arms were superior to placebo (p-value <0.0001 for both comparisons), as shown in Table 1. The estimated treatment difference in biochemical response rate at Month 12 between the OCA and placebo groups was 36% to 37% (95% CI: 23% to 24%, 49% to 50%).

Table 1. Biochemical Response and Components at Month 12, mITT Population, Trial 747-301

Parameter	OCA 10 mg N=73 n (%)	OCA Titration N=70 n (%)	Placebo N=73 n (%)
Biochemical response, n (%)	34 (47%)	32 (46%)	7 (10%)
Difference[1] (95% CI)	37% (24%, 50%)	36% (23%, 49%)	
P-value[2]	<0.0001	<0.0001	
ALP <1.67× ULN	40 (55%)	33 (47%)	12 (16%)
TB ≤1.0× ULN	60 (82%)	62 (89%)	57 (78%)
Decrease in ALP ≥15%	57 (78%)	54 (77%)	21 (29%)

Source: Statistical Review of Study 747-301, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000TOC.cfm.

[1] Difference is shown between OCA versus placebo.

[2] Two-sided p-values from the CMH test adjusted for randomization strata. Missing data were imputed as not achieving response.

ALP ULN: 118 U/L (females) and 124 U/L (males).

Total bilirubin ULN: 1.1 mg/dL (females) and 1.5 mg/dL (males).

Abbreviations: OCA, obeticholic acid;mITT, modified intent-to-treat; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with given characteristic; ALP, alkaline phosphatase; TB, total bilirubin; ULN, upper limit of normal

Summary of Safety

The main safety issues identified in Study 747-301 included liver-related adverse events, new onset of pruritus including severe pruritus, and reduction in high-density lipoprotein cholesterol (HDL-C). Subjects were not enrolled in Trial 747-301 if they had pruritus at baseline. New onset or worsening of pruritus led to dose reduction, reduction in dose frequency, drug holiday, use of antipruritic agents, and treatment discontinuation.

4.2 Trial 747-302 (Trial to Support Traditional Approval)

Trial 747-302 was intended to fulfil the PMR to verify clinical benefit of OCA in the PBC population, as a condition of accelerated approval.

4.2.1 Study Design and Statistical Methods

4.2.1.1 Study Design

Trial 747-302 was a phase 3b/4, double-blind, randomized, placebo-controlled, multicenter clinical trial evaluating the effect of OCA on clinical outcomes in subjects with PBC. The study was event driven and the final analysis was planned to occur after accrual of 127 primary endpoint events.

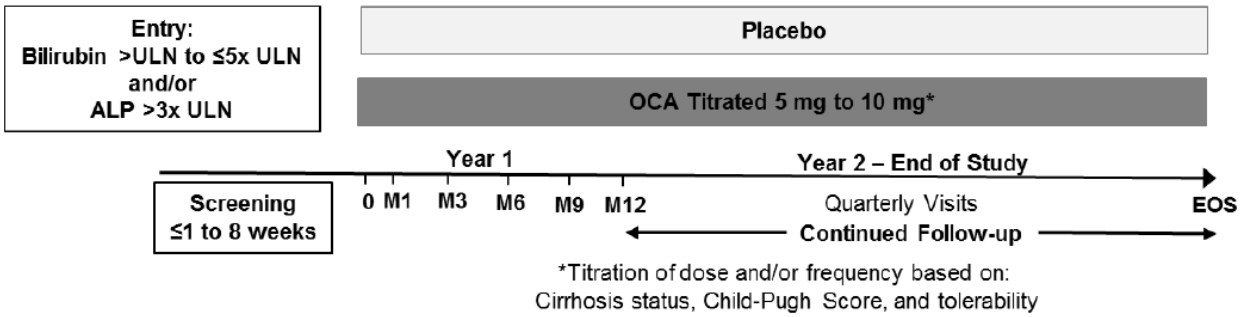
Key inclusion criteria were:

1. Age ≥18 years
2. Definite or probable PBC demonstrated by at least two of the following diagnostic factors: history of elevated ALP for at least 6 months, positive antimitochondrial titers or other specified PBC specific antibodies, or liver biopsy consistent with PBC.
3. Mean total bilirubin >ULN and ≤5× ULN and/or a mean ALP >3× ULN.
4. Either not taking UDCA (no UDCA dose in the past 3 months) or had been taking UDCA for at least 12 months with a stable dose for at least 3 months prior to Day 0.

The trial excluded subjects with concomitant liver diseases, clinical hepatic decompensation, clinical complications of PBC, or advanced disease with MELD >12.

A total of 334 subjects were randomized in a 1:1 ratio to placebo or OCA, stratified by baseline UDCA treatment use (yes/no) and baseline bilirubin categories (>ULN/ ≤ULN). The study design is shown in Figure 2.

Figure 2. Trial 747-302 Schematic



Source: Applicant Protocol Version 6 for Trial 747-302, pg. 31.
Abbreviations: ALP, alkaline phosphatase; EOS, end of study; OCA, obeticholic acid; ULN, upper limit of normal

The investigational product was taken orally, once daily for the majority of subjects. After September 2017, the starting dose and up-titration in subjects with CP B and CP C were changed. Dosing frequency was determined by the presence or absence of cirrhosis and, whether cirrhosis was present, by Child-Pugh Score, as described in Table 2.

Table 2. Dosing and Titration Regimen 747-302 Version 3.0 and Beyond

	Noncirrhotic/Child-Pugh A	Child-Pugh B or C
Starting dose	5 mg daily	5 mg weekly
Titration 1 ≥3 months	10 mg daily	5 mg twice weekly
Titration 2 ≥6 weeks after titration 1	NA	10 mg twice weekly
Titration 3 ≥6 weeks after titration 2	NA	5 mg daily (CP-B only)

Source: Clinical Protocol Amendment, Version 3 submitted by the Applicant in September 2016.
* Starting dose was determined based on presence or absence of cirrhosis and CP status at screening. Dose was up-titrated based on CP status and tolerability. In Subjects with CP B and CP C dosing was twice weekly and must be at least 3 days apart. Titration 3 was not applicable after protocol version 5.0 (January 4, 2018).

Subjects who discontinued investigational product prior to termination of the study were to continue to be followed for all regularly scheduled visits through to study closure. Subjects who discontinued investigational product but agreed to follow up either by telephone calls or review of electronic medical records were expected to continue to provide information regarding clinical outcomes or new interventions for PBC (such as initiating commercial Ocaliva). With the exception of liver transplant, if a subject experienced a suspected or confirmed clinical outcome event, the subject should have continued the regular visit schedule and continued taking the investigational product as long as the Investigator assessed that it was safe to do so.

An independent Data Monitoring Committee (DMC) was established to oversee study conduct. Three blinded adjudication committees were formed to adjudicate key safety outcomes that occurred after administration of the first dose of investigational product, as described below:

1. Cardiovascular Adjudication Committee (CAC): Adjudicated all deaths and suspected cardiovascular events (core and expanded MACE).
2. Hepatic Outcomes Committee (HOC): Adjudicated all deaths and suspected liver-related outcomes.

3. Hepatic Safety Adjudication Committee (HSAC): Blinded adjudication of potential hepatic injury and DILI and retrospective adjudication of 747-302 death or liver transplant events from the HOC database.

4.2.1.2 Efficacy Endpoints

Primary Endpoint

The initial primary endpoint was a composite endpoint of time to first occurrence of death (all-cause); liver transplant; MELD ≥15; uncontrolled ascites; or hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis; or hepatocellular carcinoma. Hepatocellular carcinoma was removed as an efficacy endpoint in protocol version 4, submitted in September 2017.

In December 2021, the definition of the primary endpoint was expanded to increase the number of clinical outcome events, in an attempt to maintain the original study power under the original assumed treatment effect size. The expanded primary endpoint for Trial 747-302 was time from randomization to the first occurrence of any of the events listed in Table 3, categorized into three groups and applicable depending on a subject's baseline disease status. The first set of events are denoted as Group 1 events. The events in **bold** typeface are the components of the primary endpoint prior to expansion.

Table 3. Expanded Primary Endpoint Events

All subjects (events are denoted Group 1 events)

• **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 polymorph leukocyte [PMNs] in the ascitic fluid)
  ○ 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 et al. 2019), portopulmonary syndrome, or hepatopulmonary syndrome) (Angeli et al. 2015)
• MELD-Na score ≥15 (for subjects with baseline MELD-Na score <12)
• **MELD score ≥15** (for subjects with baseline MELD-Na score ≥12)

Subgroup of subjects without decompensation at baseline
• 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 score ≥7 or total bilirubin >3 mg/dL
Subgroup of 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 <150×10^9/L with splenomegaly and/or with transient elastography >15 kPa

Events in **bold** comprise the primary endpoint definition before expansion.

Some events relied on biomarkers such as total bilirubin, platelets, or transient elastography. The outcome based on MELD ≥15 is a proxy for a potential need for liver transplant, i.e., disease severity has worsened to the extent that without liver transplant the participant may potentially die.

Multiplicity Controlled Secondary Endpoints (Key Secondary Endpoints)

The three key secondary endpoints evaluated subsets of events included in the primary endpoint. The second endpoint in the list was the primary endpoint prior to the expansion of the primary endpoint at the end of the trial.

1. Time to first occurrence of any Group 1 events, i.e., death, liver transplant, MELD-Na score ≥15 if MELD-Na<12 at baseline, MELD score ≥15 if MELD-Na ≥12 at baseline, uncontrolled or refractory ascites, portal hypertension syndromes (hepatorenal syndrome, portopulmonary syndrome, hepatopulmonary syndrome), or hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, or bacterial empyema
2. Time to first occurrence of death, liver transplant, MELD ≥15, uncontrolled ascites, or hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis (primary endpoint prior to expansion)
3. Time to liver transplant or all-cause death

Although this section lists the prespecified efficacy endpoints, clinical outcomes that represent a poor patient outcome, particularly liver transplant and death, can be considered to be both efficacy and safety outcomes.

4.2.1.3 Analysis Plan

The primary efficacy analysis was based on all randomized subjects who received any amount of study treatment. All 334 randomized subjects received treatment; thus, this analysis set is the same as the set of all randomized subjects, i.e., the ITT population. The safety population includes the same subjects as the ITT population.

Two intercurrent events were specified by the Applicant: (1) use of commercial OCA as concomitant medication or treatment/study visit discontinuation due to use of commercial OCA, and (2) treatment discontinuation due to other reasons. In this trial, study visit discontinuation was differentiated from the study withdrawal. If a subject discontinued investigational product and could not continue to attend regularly scheduled study visits (i.e., study visit discontinuation), the protocol stated that the subject should have been strongly encouraged to participate in study follow-up by telephone calls or electronic medical record review. For both intercurrent events, the Applicant's prespecified primary estimand targeted a treatment policy strategy such that the primary analysis includes the outcome events that occurred after the intercurrent events. For more information on estimands, refer to the Guidance for Industry, *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*.[14]

The treatment comparison was based on a log-rank test adjusted by the randomization stratification factors. Only adjudicated events were included in the analysis. The Applicant also specified presentation of the hazard ratios and 95% confidence intervals based on a Cox regression model stratified by

[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical

randomization strata to estimate the magnitude of the effect. Subjects with no data after randomization were to be censored on Day 1. Subjects who did not experience an event were censored at the time of their last contact. Last contact was the date of discontinuation from regularly scheduled study visits for subjects who did not consent to follow-up and the date of discontinuation from contact visits (medical record review / semiannual telephone calls) for patients who consented to follow-up.

A group sequential design using the O'Brien-Fleming type alpha-spending function was used to control the overall type I error rate for an interim analysis of efficacy. The interim analysis was performed at an information fraction of 0.63, corresponding to an alpha spending boundary of 0.009. The primary analysis at the end of the study was conducted at a two-sided 0.041 significance level. If the primary comparison was statistically significant, the key secondary endpoints at the final analysis were to be tested hierarchically in the order described above at a two-sided 0.041 significance level.

4.2.1.4 Categorization of the USPI-Labeled Versus USPI-Contraindicated Populations

Clinical disease severity was assessed using the past medical history at screening or randomization, baseline laboratory parameters, and clinical criteria. Any history or evidence of clinically significant portal hypertension or decompensated liver disease (Table 3) resulted in placement of the subject into the USPI-contraindicated population. Subjects who did not meet any of these criteria were adjudicated as USPI-labeled and with the current labeling would be considered the appropriate population for treatment.

Table 4. Applicant's Criteria for the USPI-Contraindicated Population in Trial 747-302

Key clinical severity criteria	
Clinically Significant Portal Hypertension	**Decompensated Liver Disease**
Transjugular intrahepatic portosystemic shunt (TIPS), variceal sclerotherapy or ligation	CP B or CP C
Hepatic venous pressure gradient (HVPG) >10 mm Hg	Gastric variceal or esophageal variceal bleeding
Paracentesis	Ascites
Thoracentesis	Hepatic hydrothorax
Collaterals secondary to CSPH	SBP
Gastrointestinal bleeding due to varices or portal HTN	Hepatic encephalopathy
Gastroesophageal varices and portal HTN	hepatorenal/ hepatopulmonary/ portopulmonary syndrome
Ascites	Prior TIPS or other peritoneal venous shunt
Hepatopulmonary syndrome	
Hepatorenal syndrome	
Portopulmonary HTN	
Hepatic encephalopathy	
Platelets $<150\times10^9$/L with splenomegaly and/or with transient elastography >15 kPa	

Source: Adapted by the Clinical Reviewer from the Applicant's CSR, Table 16.
Abbreviations: CP, Child-Pugh; CSPH, clinically significant portal hypertension; CSR, clinical study report; HTN, hypertension; SBP, systolic blood pressure; USPI, United States Prescribing Information

Limitations were noted with these determinations of the USPI-contraindicated and USPI-labeled populations due to use of nonspecific terms, for example, *medical history of portal hypertension* without

specific decompensation events recorded, which occurred in 23 subjects. However, the Agency accepted the Applicants' categorization for analysis purposes.

4.2.2 Patient Disposition and Exposure

4.2.2.1 Patient Disposition

In Trial 747-302, a total of 334 subjects were randomized at 116 sites in 27 countries. The trial was conducted from December 26, 2014 (date of provision of informed consent by the first subject) to December 23, 2021 (date of last visit of the last subject).

As the efficacy analyses were prespecified to be conducted in the ITT population (i.e., including both the USPI-labeled and USPI-contraindicated populations), the Agency evaluated the subject characteristics and efficacy results separately in the ITT and USPI-Labeled populations.

Baseline demographics in Trial 747-302 were generally balanced across the treatment groups in the ITT and USPI-labeled populations (Table 23 in Section 8.3.2). The majority of subjects in the ITT population was white (86.5%), non-Hispanic (82.9%), and female (89.8%). The average age was 53.7 years. Approximately 18% of the subjects were from the United States. Baseline disease severity variables were comparable across treatment arms in the ITT and USPI-labeled populations (Table 5 and Table 23 in Section 8.3.2).

Table 5. Baseline Clinical Characteristics, ITT Population, Trial 747-302

Characteristic	OCA N=168 n (%)	Placebo N=166 n (%)	Total Population N=334 n (%)
Baseline disease stage per USPI[1], n (%)			
USPI-labeled	81 (48.2%)	68 (41.0%)	149 (44.6%)
USPI-contraindicated	87 (51.8%)	98 (59.0%)	185 (55.4%)
Baseline disease stage, n (%)			
Noncirrhotic	78 (46.4%)	62 (37.3%)	140 (41.9%)
Compensated cirrhosis	58 (34.5%)	67 (40.4%)	125 (37.4%)
Decompensated cirrhosis	32 (19.0%)	37 (22.3%)	69 (20.7%)
Baseline Rotterdam criteria, n (%)			
Early	55 (32.7%)	51 (30.7%)	106 (31.7%)
Moderate	102 (60.7%)	104 (62.7%)	206 (61.7%)
Advanced	11 (6.5%)	11 (6.6%)	22 (6.6%)

Source: Clinical Study Report 747-302 (pp. 115-116); findings reproduced by the statistical reviewer using adsl.xpt.
[1] As defined by the Applicant.
Abbreviations: ITT, intent-to-treat; OCA, obeticholic acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation

As expected, there were differences in laboratory and clinical parameters between the USPI-labeled and USPI-contraindicated populations. The USPI-contraindicated population had more subjects with moderate or advanced disease per the Rotterdam criteria and CP class B PBC subjects, as well as higher baseline MELD scores, lower baseline platelet counts, or had a higher total bilirubin (See Table 23 in Section 8.3.2).

The summary of disposition of trial subjects in the ITT population is provided in Table 6. Disposition for the USPI-labeled population is presented in Table 24 in Section 8.3.3. The percentage of subjects who remained in the trial until trial closure was similar across the two treatment arms (~51%). Withdrawal by subject was the most frequently recorded reason for early discontinuation from the trial in both

treatment arms. The percentages of subject withdrawal were similar in the two arms. A greater percentage of placebo-randomized patients subjects (6.0%) compared to OCA-randomized subjects (1.2%) discontinued the trial due to physician decision.

A total of 31% of OCA subjects and 22% of placebo subjects in the ITT population were still taking study drug at the time of trial closure. The most common reason for treatment discontinuation was an adverse event (OCA 38.7% versus placebo 30.7%). There were more subjects in the placebo arm than in the OCA arm who discontinued treatment due to initiation of commercial OCA (OCA 6.5% versus placebo 14.5%). A difference between the treatment arms was also observed in the rate of discontinuation of treatment due to physician decision.

Table 6. Patient Disposition, ITT Population, Trial 747-302[1]

Parameter	OCA N=168 n (%)	Placebo N=166 n (%)	Total Population N=334 n (%)
On study at time of study closure	88 (52.4%)	83 (50.0%)	171 (51.2%)
Discontinued trial			
Adverse event	9 (5.4%)	10 (6.0%)	19 (5.7%)
Death	14 (8.3%)	10 (6.0%)	24 (7.2%)
Lost to follow-up	7 (4.2%)	8 (4.8%)	15 (4.5%)
Initiated commercial OCA	4 (2.4%)	2 (1.2%)	6 (1.8%)
Withdrawal by subject	27 (16.1%)	30 (18.1%)	57 (17.1%)
Physician decision	2 (1.2%)	10 (6.0%)	12 (3.6%)
Site closure	3 (1.8%)	5 (3.0%)	8 (2.4%)
COVID-19 limitation	3 (1.8%)	-	3 (0.9%)
Noncompliance with study drug	1 (0.6%)	-	1 (0.3%)
Other	10[a] (6.0%)	8[b] (4.8%)	18 (5.4%)
On study drug at time of study closure	52 (31.0%)	37 (22.3%)	89 (26.6%)
Discontinued study drug			
Adverse event	65 (38.7%)	51 (30.7%)	116 (34.7%)
Initiated commercial OCA	11 (6.5%)	24 (14.5%)	35 (10.5%)
Physician decision	7 (4.2%)	17 (10.2%)	24 (7.2%)
Noncompliance with study drug	3 (1.8%)	2 (1.2%)	5 (1.5%)
Protocol violation	-	2 (1.2%)	2 (0.6%)
Site closure	4 (2.4%)	2 (1.2%)	6 (1.8%)
COVID-19 limitation	3 (1.8%)	-	3 (0.9%)
Death	1 (0.6%)	-	1 (0.3%)
Withdrawal by subject	17 (10.1%)	20 (12.0%)	37 (11.1%)
Lost to follow-up	1 (0.6%)	4 (2.4%)	5 (1.5%)
Other	4[c] (2.4%)	7[d] (4.2%)	11 (3.3%)

Source: Clinical Study Report 747-302 (Page 255-256); findings reproduced by the statistical reviewer using adsl.xpt

[1] Duration was up to study termination by the Applicant.

[a] Five subjects: liver transplant, one subject: liver transplant waitlist, one subject: noncompliance, one subject: patient started another intervention study, one subject: PI decision – hepatic decompensation, one subject: withdrew consent.

[b] Four subjects: liver transplant, two subjects: liver transplant waitlist, one subject: study close-out, one subject: missing.

[c] Two subjects: Per Applicant request due to label change, one subject: subject was randomized without meeting all eligibility criteria, one subject: liver transplant.

[d] Two subjects: Per Applicant request due to label change, three subjects: disease progression, two subjects: liver transplant waitlist.

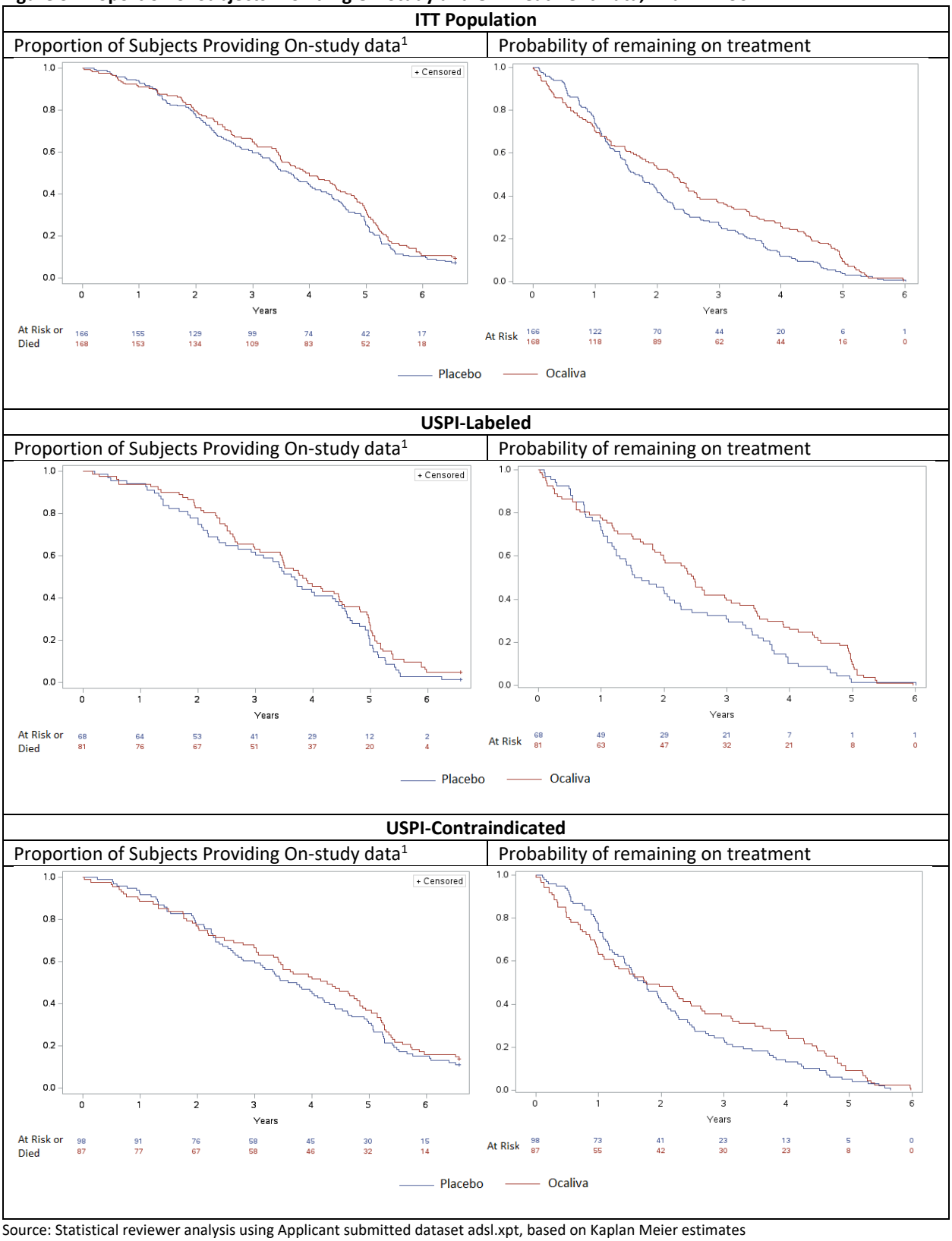
Abbreviations: OCA, obeticholic acid; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group

To better understand the timing of on-treatment and on-study, Figure 3 displays the Kaplan-Meier estimates of the proportion of subjects providing on-study data (left panels) and on-treatment data

(right panels) over time in the ITT, USPI-labeled, and USPI-contraindicated populations. In all populations considered (ITT, USPI-labeled, and USPI-contraindicated), the two arms provided similar Kaplan-Meier estimates when considering on-study data (left panels), though there is some more study discontinuation in the placebo arm compared to the OCA arm in the middle years of the study.

When considering on-treatment data (right panels), the Kaplan-Meier curves cross in each of the plots, indicating that there was more treatment discontinuation in the OCA arm in the early part of the trial and more treatment discontinuation in the placebo arm in later years.

Figure 3. Proportion of Subjects Providing On-Study and On-Treatment Data, Trial 747-302



Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt, based on Kaplan Meier estimates

[1] Deaths are censored at the end of the trial, as death is not a mechanism of generating missing data and these subjects provided full information on their outcome information.

4.2.2.2 Extent of Exposure

The mean (SD) duration of exposure in Trial 747-302 to OCA and placebo was as follows – for OCA (168 subjects) 29.5 months and for placebo (166 subjects) 25.1 months. See Table 7.

Table 7. Duration of Exposure, Safety Population, Trial 747-302

Parameter	Total OCA N=168 n (%)	Total Placebo N=166 n (%)
Duration of treatment, months		
Mean (SD)	29.5 (21.3)	25.1 (17.3)
Median (Q1, Q3)	27.1 (10.4, 48.6)	20.2 (12, 36.5)
Min, max	0.1, 71.7	1.1, 72.1
Total exposure (patient-years)	413	347

Source: CDS adex.xpt and adsl.xpt; Software: R Duration is up to 2196 days.

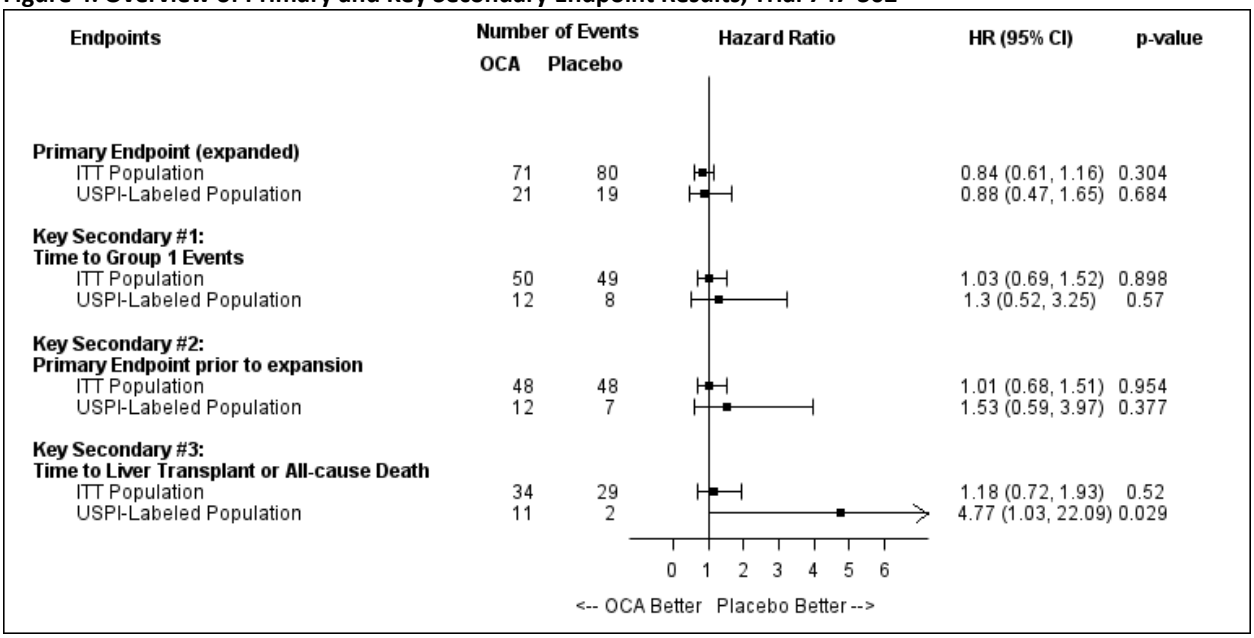
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OCA, obeticholic acid; Q1, first quartile; Q3, third quartile; SD, standard deviation

4.2.3 Efficacy Results

The summary of efficacy analysis results for the prespecified primary and key secondary endpoints are presented in Figure 4. An HR less than 1 indicates a trend of benefit for OCA, and an HR greater than 1 indicates a trend of harm for OCA. Trial 747-302 failed to meet its primary endpoint in the ITT population (HR=0.84, 95% CI: 0.61, 1.16], p-value=0.304). The magnitude of the estimated treatment effect on the primary endpoint was similar in the USPI-labeled population (HR=0.88, 95% CI: 0.47, 1.65). As the primary endpoint failed to achieve statistical significance, there is no alpha remaining to test other endpoints and all other p-values presented are nominal.

As the endpoints become more focused on the more severe events (i.e., moving down Figure 4), the point estimate of the HR moves from less than 1 (favoring OCA) to greater than 1 (favoring placebo). For the time to liver transplant or all-cause death endpoint, there was a trend of harm of OCA in the ITT population (HR=1.18, 95% CI: 0.72, 1.93). There was also a trend of harm of OCA in the USPI-labeled population, with an estimated hazard ratio of 4.77 and a 95% confidence interval not containing 1 (95% CI: 1.03, 22.09).

Figure 4. Overview of Primary and Key Secondary Endpoint Results, Trial 747-302



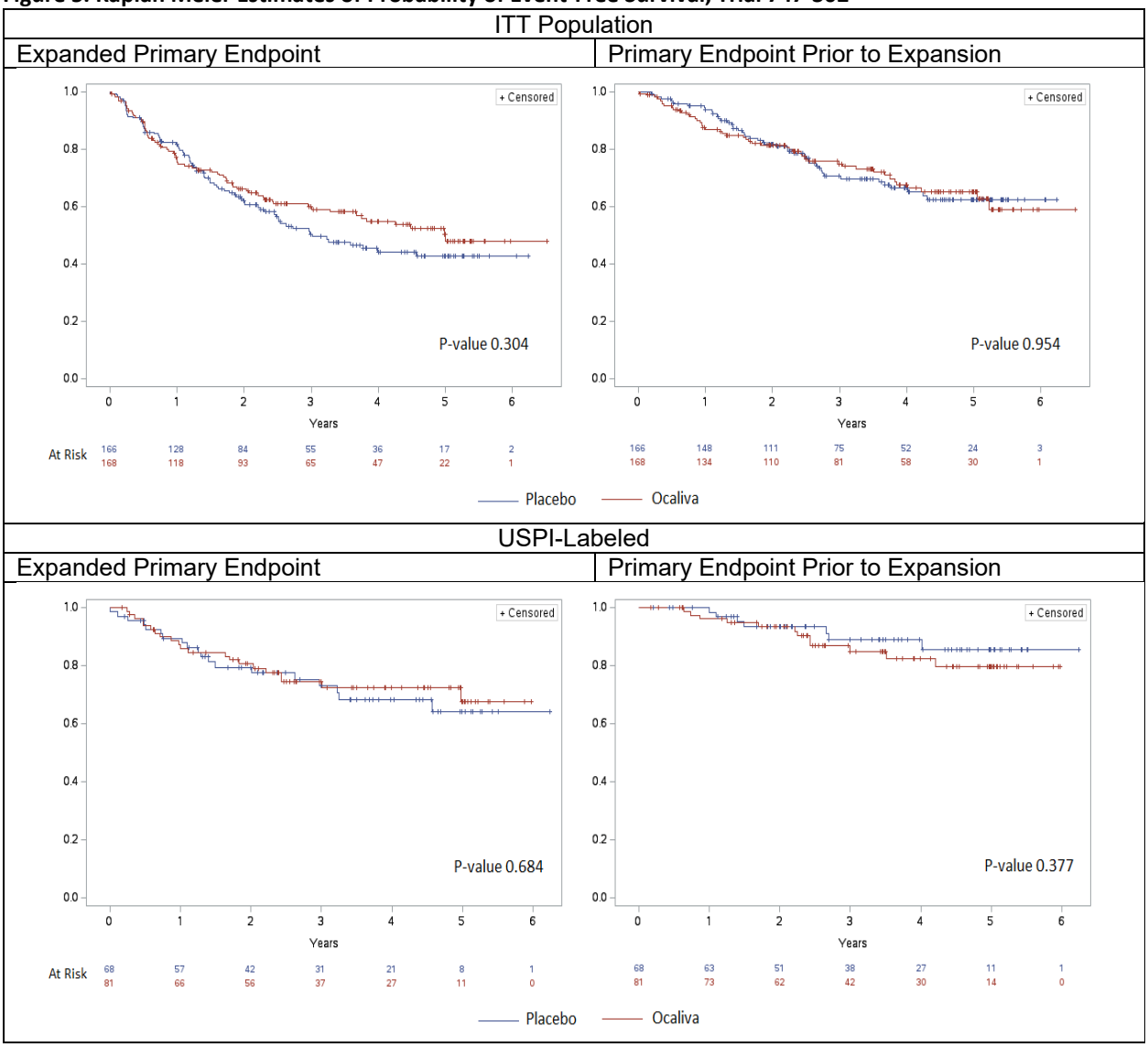
Source: Statistical reviewer's analysis using adtte.xpt and adsl.xpt; Results aside from key secondary endpoint #3 in ITT population match Applicant's results in Clinical Study Report 747-302 (pages 432, 433, 589, 590, 612, 613, 639, 640).
Total sample size for ITT population: OCA, N=168; placebo, N=166
Total sample size for USPI-labeled population: OCA, N=81; placebo, N=68
The hazard ratio and 95% CI are determined based on a Cox regression model stratified by randomization strata. HR <1 indicates trend of benefit for OCA, >1 indicates trend of harm for OCA. The p-value is from the log rank test stratified by the randomization stratification factors. The Applicant's analysis of time to liver transplant or death in the ITT population excluded two deaths on the OCA arm and one death on the placebo arm. The Applicant responded to an Information Request that the "events occurred more than 30 days after the patients had withdrawn consent for follow-up" were not included in their analyses. However, this "end of study plus 30 days" criterion was not specified in the protocol nor the Statistical Analysis Plan. The Applicant's analysis resulted in a hazard ratio of 1.15 (95% CI: 0.69, 1.91) with nominal p-value of 0.594.
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OCA, obeticholic acid; USPI, United States Prescribing Information

To assess efficacy over time, Kaplan-Meier estimates of the probabilities of event-free survival, as defined for the both the expanded primary endpoint and the primary endpoint prior to expansion are displayed in Figure 5 for the ITT and USPI-labeled populations (for additional information, see Table 28 in Section 8.3.6). The Kaplan-Meier curves cross in each of the plots.

For the ITT population, there is some separation of the curves for the expanded primary endpoint after 1 year, with the OCA arm performing better; this separation of curves is not maintained for the primary endpoint prior to the expansion, which includes more severe clinical outcomes.

For the USPI-labeled population, there is some separation of curves for the expanded primary endpoint around Year 3, with the OCA arm performing better; however, for the primary endpoint prior to the expansion, there is some separation of the curves with a trend towards harm of OCA.

Figure 5. Kaplan Meier Estimates of Probability of Event-Free Survival, Trial 747-302



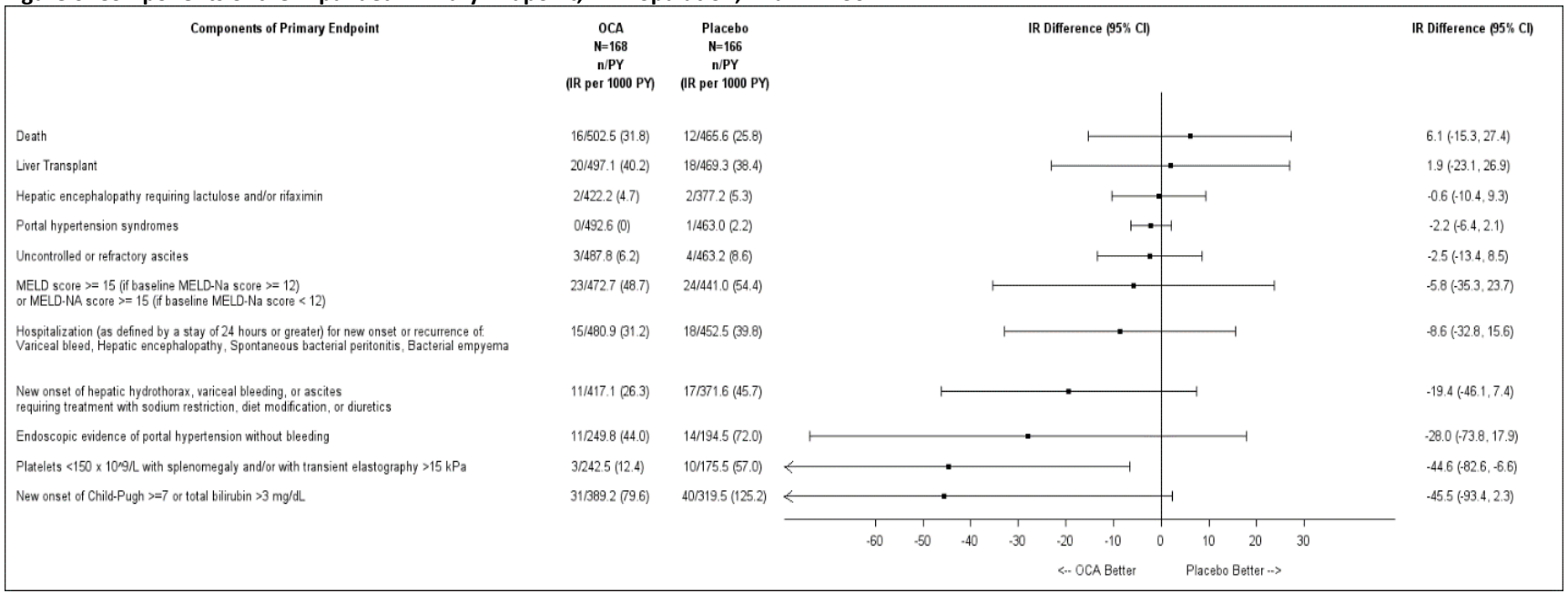
Source: Statistical reviewer analysis using Applicant submitted dataset adtte.xpt, based on Kaplan Meier estimates.
P-values based on the log rank test stratified by the randomization stratification factors.
Abbreviations: ITT, intent-to-treat; USPI, United States Prescribing Information

Given the trend towards benefit observed in the expanded primary endpoint and the trends toward harm observed on the key secondary endpoints, particularly in the USPI-labeled population, the components of the expanded primary endpoint were further explored to assess the outcomes of individual components. Figure 6 presents the incidence rates (IRs) of each component of the expanded primary endpoint for the ITT population; this includes subjects who experienced each event at any time in the study, regardless of whether another primary endpoint event occurred prior. Figure 11 shows these data for the USPI-labeled population; similar trends are evident.

The placebo arm had higher incidence rates for components that are reliant on biomarkers, i.e., laboratory values that may fluctuate over the disease course (e.g., bilirubin, platelet count) or imaging markers (transient elastography score), along with several clinical outcomes with subjective assessment

(e.g., ascites or hepatic encephalopathy categories in Child Pugh score). The OCA arm had higher incidence rates for liver transplant and death, which were well defined and captured.

Figure 6. Components of the Expanded Primary Endpoint, ITT Population, Trial 747-302



Source: Statistical reviewer analysis using Applicant submitted dataset adevt,xpt and adsl.xpt.

[1]According to the Applicant, if an expanded endpoint components trigger occurred after any positively adjudicated endpoint event, the trigger was not sent for adjudication. Thus, the expanded endpoint components may not be reliably captured in this analysis.

[2]The incidence rate (IR) is calculated by dividing the number of subjects who experienced the event by the total number of patient-years (PYs) of at-risk time and multiplying by 1000. At-risk time for a subject who experienced an event is time from randomization to the first event, and at-risk time for a subject who did not experience an event is time from randomization to end of study.
Analysis of each component ignores the occurrence of other components and important intercurrent events (e.g., deaths)

[3] IR difference is calculated by subtracting the IR of events in the placebo arm from the IR of events in the OCA arm

The 95% confidence interval was calculated based on normal approximation and $\hat{\sigma}(IR) = \sqrt{n/PY^2}$

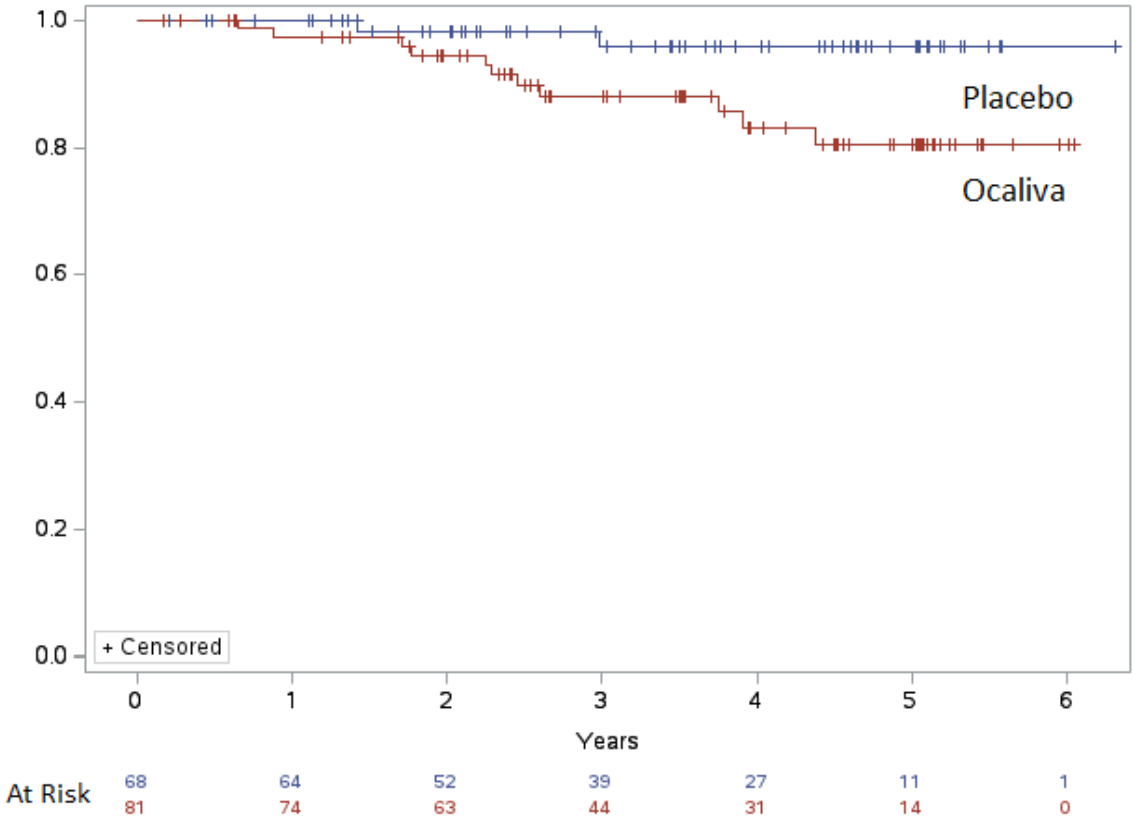
Abbreviations: OCA, obeticholic acid; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with event; PY, patient-year; IR, incidence rate

4.2.4 Liver Transplant and Death

4.2.4.1 Liver Transplant and Death (USPI-Labeled Populations)

The Kaplan Meier plot of transplant-free survival in the USPI-Labeled population (Figure 7) shows separation between the two treatment arms, with the OCA arm having a lower estimated probability of surviving without liver transplant compared to the placebo arm (HR=4.77, 95% CI: 1.03, 22.09). See the results of the key secondary endpoint of time to liver transplant or all-cause death in Figure 4.

Figure 7. Probability of Transplant-Free Survival, USPI-Labeled Population, Trial 747-302

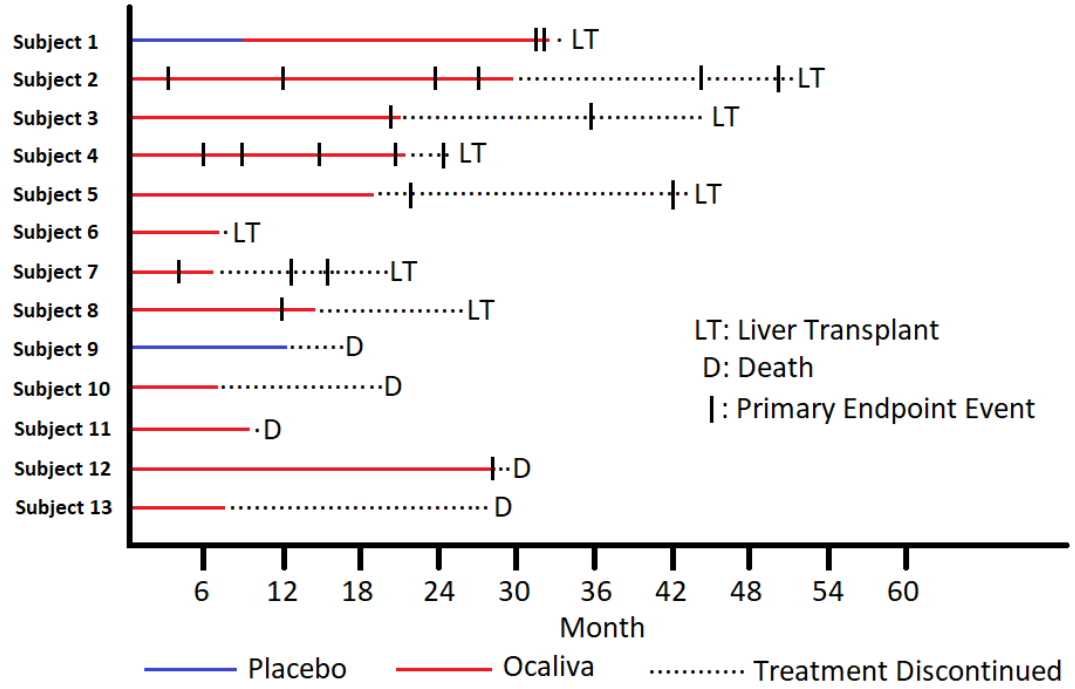


Source: Statistical reviewer's analysis using Applicant submitted dataset adtte.xpt, based on Kaplan-Meier estimates.
Abbreviation: USPI, United States Prescribing Information

To evaluate the trial experience of subjects in the USPI-labeled population who experienced liver transplant or death, the subject-level trajectories are presented in Figure 8. Blue lines represent use of placebo, and red lines represent use of OCA (study-provided or commercially available). Dotted lines represent treatment discontinuation, and vertical lines represent any other primary endpoint events. The earliest liver transplant and death occurred in OCA-treated subjects 8 months after initiating treatment (subject 6) and 10 months after initiating treatment (subject 11), respectively. The only liver transplant observed in the placebo arm (subject 1) occurred in a subject who was taken off placebo (without a noted adverse event or clinical change), and 1 day later started commercial OCA and progressed to decompensated cirrhosis with portal hypertensive complications. The patient required transplant after 2 years on commercial OCA therapy.

Most subjects who experienced liver transplant or death in the OCA arm also experienced other primary endpoint events (e.g., hepatic decompensation) earlier in the study while on-treatment. Subject 2 underwent liver transplant 4.3 years after starting OCA but experienced the first decompensation event at Month 3. Subject 7 underwent liver transplant 1.7 years after starting OCA but experienced the first decompensating event at Month 4.

Figure 8. Subject Trajectory of USPI-Labeled Population Who Experienced Liver Transplant or Death, Trial 747-302



Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt and adtte.xpt.
Blue line represents placebo, red line represents OCA, either study-provided or commercially available.
Dotted line represents treatment discontinuation, and vertical lines represent any other FDA primary endpoint events (Table 3 or Table 2 CSR).
Abbreviations: D, death; LT, liver transplant; OCA, obeticholic acid; USPI, United States Prescribing Information

4.2.4.2 Deaths: Subject-Level Details

In the overall population of Trial 747-302, a total of 28 deaths were reported; 16 of OCA-treated subjects and 12 of placebo-treated subjects. The causes of death are listed in Table 32.

The number of deaths reported in the USPI-labeled population was higher in the OCA treatment arm (n=4) compared to the placebo treatment arm (n=1). The causes of death in the four USPI-labeled OCA treated subjects were due to the following AEs : subdural hematoma (n=1); lymphoma (n=1); multiorgan failure (n=1); and liver-related death (n=1); this case is described below. The death in the USPI-labeled placebo treated subject was due to cardiopulmonary arrest (n=1).

One OCA-treated subject who died due to a liver-related cause had baseline laboratory values of TB 2 mg/dL, ALT 155 U/L, ALP 453 U/L, platelet count 224×10^9/L, and MELD score 9.1. An upper endoscopy on Day 3 showed esophagitis and gastritis but no evidence of esophageal varices. On Day 378, upper endoscopy showed large esophageal varices with hypertensive gastropathy, however, she continued to receive OCA. On Day 889, the subject presented with a recurrent upper gastrointestinal hemorrhage.

She subsequently had three further episodes of gastrointestinal hemorrhage, which included hematochezia, anemia, with hematemesis, hypovolemic shock, and cerebral edema, followed by cardiopulmonary arrest. She died on Day 937. The hepatic outcomes committee adjudicated this event as a liver-related death. The subject was classified as non-cirrhotic (USPI-labeled population) had progression to cirrhosis 1 year after initiating OCA and died 2.5 years after initiating OCA.

Conclusion: Numerically, more deaths occurred in the OCA-treated subjects compared to the placebo-treated subjects in the USPI-labeled population. A USPI-labeled, OCA treated noncirrhotic subject died (due to liver-related event). At baseline, this subject had a baseline MELD score of 8.4, laboratory parameters within the normal ranges, and was otherwise stable, and a rapid progression of disease with hepatic decompensation was not expected.

4.2.4.3 Hepatobiliary Injury

4.2.4.3.1 Review Issue and Background (OCA-Mediated Hepatotoxicity)

We explore whether the hepatobiliary injury, which encompasses drug-induced liver injury (DILI) including cholestatic injury that can mimic progression of underlying liver disease. We also analyzed whether hepatobiliary injury could have been predicted and the risk mitigated.

OCA has been associated with DILI. DILI occurred in patients with PBC, patents exposed to OCA with nonalcoholic steatohepatitis (NASH)/metabolic associated steatohepatitis (MASH), and healthy volunteers. DILI can be hepatocellular, cholestatic, or mixed. The mechanisms by which OCA is postulated to lead to liver injury include: (1) direct injury due to cholestasis, (2) accumulation of biliary sludge leading to an increased risk of gallstones, choledocholithiasis, and cholangitis. The mechanisms of hepatocellular and mixed DILI are unclear. DILI is both dose-dependent (particularly in subjects with advanced cirrhosis) and non-dose-related in noncirrhotic and compensated cirrhotic subjects.

OCA has higher hydrophobicity compared to endogenous primary bile acids. Hydrophobic bile acids are considered more toxic to the liver compared to hydrophilic ones; this may be a mechanism by which OCA increases the risk of liver injury (van Golen et al. 2018; Wang et al. 2009) and the risk of gallstone formation (Al-Dury et al. 2019).

Protocol prespecified safety assessments (laboratory analysis and clinical examination) in Trial 747-302 occurred at baseline, Months 1, 2, and 3, and then 3 3 months until the end-of-trial. All subjects had a CP score computed at baseline, however, the criteria for dosing, dose adjustment, or discontinuation were applied only if cirrhosis was determined by protocol-defined criteria. Change in CP status, MELD score, and AEs were evaluated during scheduled follow-up visits. Progression to cirrhosis was assessed every 6 months using transient elastography, platelet count, ELF test, and APRI score. If liver injury was suspected, then liver tests were to be collected at the local laboratory and results were recorded. The CP score was calculated every 6 months and if the status changed, i.e., patient progressed to CP B or CP C while the subject was in the clinical trial, the OCA dosage was to be reduced per the protocol (Table 2).

In the ITT population, a total of 38 subjects received liver transplants, 20 in the OCA treatment group and 18 in the placebo group. Of the 38 liver transplant recipients, 30 (79%) subjects were in the USPI-contraindicated population, which is consistent with the more advanced liver disease in this population. See the baseline demographics in Section 8.3.2, Table 23.

In Trial 747-302, a total of eight subjects required liver transplant in the USPI-labeled population. Seven of these eight subjects received OCA. One subject (Subject 1) who received placebo initially, later

switched to commercial OCA (cOCA), remained on cOCA from Days 269 to 985, and received a liver transplant on Day 1078. PK levels obtained on Day 365 were also positive for OCA in this subject while the subject was in the trial. Six of the eight liver transplant cases had been adjudicated as noncirrhotic at baseline (Table 28 in Section 8.3.7). The reason for the switch from placebo to cOCA may have been worsening of fatigue; however, changes in laboratory parameters or clinical status were not noted.

The baseline laboratory and key clinical parameters of the eight subjects who received liver transplant were as follows:

The Applicant identified six of the eight subjects as noncirrhotic who received liver transplant in Trial 747-302. The mean CP A score was 5.3 (range 5 to 6). Six subjects had TB <2× ULN, and the mean TB was 1.7 mg/dL (range 0.6 to 2.6 mg/dL). The mean platelet count was 234 (range 139 to 373) and the mean MELD score was 8.4 (range 6.4 to 9.7). The mean ALT was 121 (range 40 to 224) and the mean liver stiffness score was 11.8 (range 7.8 to 14.7). All the subjects were categorized as CP A by the Applicant. Regardless of the presence of cirrhosis, all subjects were assigned a CP score, i.e., noncirrhotic subjects were categorized as CP A. Liver biopsy is generally not performed in this population to confirm the presence of cirrhosis.

Laboratory, imaging, and clinical biomarkers at baseline suggest that most subjects did not have compensated cirrhosis with portal hypertension (i.e., advanced disease) or HI. Given the slow progression of disease, one would not have predicted an event of decompensation or the need for liver transplant.

Most subjects required liver transplant for worsening of liver function and decompensation, except two subjects in whom pruritus was noted as the indication for liver transplant.

4.2.4.3.2 Assessment for DILI

In Trial 747-302, the Applicant's independent Hepatic Safety Adjudication Committee (HSAC), the members of which were blinded to treatment, retrospectively adjudicated all cases of liver injury, and assessed for causality i.e., event relatedness to study drug (DILI). The HSAC members assessed if evidence of liver injury existed and if so, whether it was due to another cause (e.g., muscle injury, laboratory error). If the suspected liver injury was adjudicated as a DILI, then causality and severity assessments were performed.

Scoring of DILI cases for causality assessment was performed as follows: insufficient information (insufficient details in case package), unlikely drug related (if confidence of causality assessment was <25%); possible drug related (if confidence of causality assessment was 25% to 49%); probable drug related (if confidence of causality assessment was 50 %to 74%); and highly likely drug related (if confidence of causality assessment was 75% to 100%) (as noted in the HSAC Charter version 8.8; March 1, 2023, Table 5.2.1).

4.2.4.3.2.1 DILI Adjudication

A total of 26 cases (27 events) were adjudicated by the HSAC as possible (n=26) or probable (n=1) qualifying as events of liver injury (Table 8). Of these possible or probable cases of DILI related to investigational product use, 22 of 27 (81.5%) were in the USPI-contraindicated population. One case (one event) adjudicated by HSAC as a probable DILI was in a subject in the USPI-contraindicated group and had evidence of portal hypertension. DILI adjudication was complicated by the underlying advanced disease and confounded by disease progression in the USPI-contraindicated population.

Five cases of possible DILI occurred in the USPI-labeled population. Four of the five cases were in OCA-treated subjects and one was in a placebo-treated subject. Of these four DILI events in the OCA-treated subjects, the Agency adjudicated three to be related to OCA use and one to be unrelated. One case of possible DILI is summarized below; the other two are described in the Appendix.

Table 8. Blinded DILI Assessments for Events of Liver Injury by HSAC, USPI Labeled, USPI-Contraindicated, and Overall Safety Population

HSAC DILI Adjudication for the USPI-Labeled Population		
	OCA (n=81)	**Placebo (n=68)**
Possible DILI	4 (4.9%)	1 (1.5%)
HSAC DILI Adjudication for the USPI-Contraindicated Population		
	OCA (n=87)	**Placebo (n=98)**
Probable DILI	1 (1.1%)	0 (0%)
Possible DILI	13 (14.9%)	7 (7.1%)
HSAC DILI Adjudication for the Overall Safety Population		
	OCA (n=168)	**Placebo (n=166)**
Probable DILI	1 (0.59%)	0 (0%)
Possible DILI	17 (10%)	8 (4.8%)
TOTAL	**18 (10.7%)**	**8 (4.8%)**

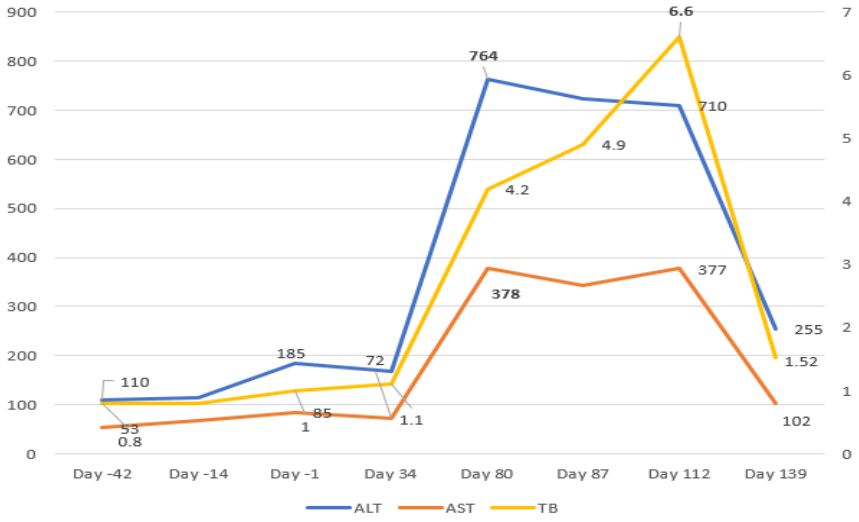
Source: Reviewer generated from data submitted by the Applicant; blinded HSAC DILI assessments for liver injury events (numbers and percentages within arm) on the OCA and placebo arms.
Abbreviations: DILI, drug-induced liver injury; HSAC, Hepatic Safety Adjudication Committee; OCA, obeticholic acid; USPI, United States Prescribing Information

4.2.4.3.2.2 Subject 14 With DILI Event Adjudicated as Possible DILI

A 45-year-old female diagnosed with PBC in 2013, diagnosis confirmed by liver biopsy in 2013. Liver biopsies were obtained in 2013 and 2016, both of which showed no evidence of AIH overlap. The subject's past medical history was relevant for hypertension, pruritus, Sjogren's syndrome, arthritis, and hypercholesterolemia. Prior to enrollment in the trial, the patient was taking ethinylestradiol/levonorgestrel, UDCA, hydroxyzine, prednisone 5 mg (arthritis), omeprazole, simvastatin, and lactulose (for constipation).

She started OCA 5 mg per day and experienced increased pruritus, which required dose reduction to every other day on Day 9. On Day 37, she resumed daily dosing. On Day 51 an ultrasound revealed cholelithiasis, but no symptoms were reported at that time. On Day 81, abnormal liver tests were noted with marked elevations in ALT, AST, and TB. The investigator noted "no other suspected cause" and classified this event as "severe" and "definitely" related to study medication. Study drug was discontinued on Day 89. On Day 122, the subject underwent an elective cholecystectomy with subcapsular liver biopsy, which showed extensive ductopenia and variable portal inflammation.

Figure 9. DILI Case Review: Liver Tests Over the Trial Timeline



Study Day	Day -42	Day -14	Day -1	Day 34	Day 80	Day 87	Day 112	Day139
ALT	110	115	185	168	764	724	710	255
AST	53	67	85	72	378	342	377	102
ALP	534	527	574	440	460	479	446	688
TB	0.8	0.8	1	1.1	4.2	4.9	6.6	1.52

Source: Generated by the Clinical Reviewer using data submitted by the Applicant in AdaM datasets.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin

4.2.4.3.3 Conclusion

PBC is a cholestatic disease and hepatotoxicity secondary to OCA can also present as cholestatic injury, i.e., OCA-induced hepatobiliary toxicity mimics progression of the underlying PBC. Therefore, a comparison of the OCA and placebo groups in Trial 747-302 offers evidence of an association of OCA use with hepatotoxicity.

In the USPI-labeled population, 11 OCA participants died or had a liver transplant versus 2 placebo participants, resulting in OCA-exposed subjects having a lower estimated probability of surviving without liver transplant compared to those who received placebo (HR=4.77, 95% CI 1.03, 22.09). Six of the eight subjects who had liver transplant were noncirrhotic at baseline. The USPI-labeled subjects at baseline had early-stage disease and based on the indolent nature of disease (PBC) progression, these subjects were not expected to progress to a need for liver transplant or die during the clinical trial.

DILI events occurred in a larger number of subjects in the USPI-contraindicated population compared to the USPI-labeled population. In the USPI-labeled population, DILIs adjudicated as possible DILIs by the independent HSAC occurred in 4.9% of OCA-treated subjects compared to 1.5% of placebo-treated subjects. Clinically, DILIs in the OCA-treated subjects were characterized by marked elevations in ALT and AST with and without jaundice as well as with isolated alkaline phosphatase elevations, i.e., the DILI signature was hepatocellular, cholestatic, and mixed.

4.2.4.4 Pruritus

4.2.4.4.1 Issue

Pruritus is a known adverse reaction of OCA. The mechanism by which OCA causes pruritus is unknown.

Protocol prespecified criteria for dose adjustment, interruption, discontinuation, or rechallenges for pruritus were managed either (1) new-onset severe pruritus was managed with a drug holiday; or (2) less-frequent dosing with return to the original USPI-recommended dose as tolerated.

4.2.4.4.2 Assessment

New onset or worsening of pruritus and pruritus leading to treatment discontinuation occurred more often in the OCA arm compared to the placebo arm, with an IR difference of 63.7 (95% CI: 37.5, 93.6) and 4.3 (95% CI: 0.1, 8.8), respectively, in the Safety Population (calculated as on-trial[15]).

The incidences of pruritus requiring treatment, severe pruritus, pruritus requiring treatment discontinuation, and SAE of pruritus were higher among OCA-treated subjects compared to placebo-treated subjects in the overall safety and USPI-labeled populations. See Table 9.

Table 9. Adverse Events Related to Pruritus; Safety Population and USPI-Labeled Population, Trial 747-302

Population	Total OCA	Total Placebo	IR Difference (95% CI)
	N=168	N=166	
Overall safety population	n/PY (IR)	n/PY (IR)	
Pruritus requiring treatment	90/234.4 (38.39)	48/323.78 (46.5)	23.57 (14.59, 32.54)
Severe pruritus	50/368.40 (13.57)	19/387.23 (4.91)	8.66 (4.30, 13.03)
Pruritus requiring treatment discontinuation	20/459.18 (4.36)	3/420.53 (0.71)	3.64 (1.57,5.72)
SAE of pruritus	2/475.01 (.04)	0/426.46 (0)	0.42 (-0.162, 1.00)
USPI-labeled population	N=81	N=68	IR difference (95% CI)
	(n/PY (IR)	n/PY (IR)	
Pruritus requiring treatment	47/116.48 (40.35)	19/142.83 (13.30)	27.05 (14.05,40.04)
Severe pruritus	25/182.75 (13.68)	10/159.29 (6.28)	7.40 (0.78,14.03)
Pruritus requiring treatment discontinuation	12/231.23 (5.19)	2/175.84 (1.14)	4.05 (0.72,7.39)
SAE of pruritus	1/241.41 (0.41)	0/180.84 (0)	0.41 (-0.40,1.23)

Source: Modified from Applicant Information Request Response Table 24.3 August 6, 2024.
Abbreviations: CI, confidence interval; IR, incidence rate; PY, patient-year; SAE, serious adverse event

4.2.4.4.3 Conclusion

Although pruritus is commonly associated with PBC, the pathophysiology of the effect of OCA on worsening of pruritus is unclear.

New onset pruritus or worsening of pruritus was the most common AE in subjects administered OCA. Pruritus was also the most common cause of treatment discontinuation in the OCA arm compared to the placebo arm. Furthermore, pruritus led to dose modification, decrease in dosing frequency, treatment interruption, use of antipruritic pharmacological interventions (prescribed and over the counter), and permanent treatment discontinuation, and was reported as an indication for liver transplantation. More than 50% of the OCA-treated subjects required an additional treatment to ameliorate pruritus.

4.2.5 Interpretability of Trial 747-302

The Applicant claims that Trial 747-302 was underpowered and that the results from Trial 747-302 are uninterpretable due to the following sources of bias:

- Functional unblinding and informative censoring
- Initiation of commercial PBC therapies
- Differential data collection

[15] On-trial period was defined as duration of subject follow-up until the end-of-trial.

Following its analysis, the Agency found that Study 747-302 provides meaningful, interpretable data to draw conclusions for safety and clinical effectiveness and informs the benefit-risk of OCA. The Agency addresses the Applicant's four concerns as follows.

4.2.5.1 Power

In the NDA submission, the Applicant claims that the study was underpowered with "post hoc power <0.8 for hazard ratio of >0.63." However, as stated by the Applicant on December 22, 2021:

> "Being an event driven study, a number of events was to be reached to warrant study closure. The orderly closure of the study at that time has been built into the protocol design. With the expanded endpoints, as agreed with the Agency in the revised SAP, the predefined number of endpoints is assumed to be reached triggering closure."

Trial 747-302 was an event-driven trial that required at least 127 events to achieve 80% power with an assumed hazard ratio of 0.6, the effect size assumed by the Applicant. This power calculation was not updated by the Applicant upon expansion of the primary endpoint definition. Using the previous definition of the primary endpoint, 96 events were observed; with the expanded primary endpoint definition, 151 events were observed, exceeding the 127 events required to achieve 80% power under the assumption that HR=0.6.

4.2.5.2 Functional Unblinding and Informative Censoring

The Applicant stated that the relationship between ALP levels and IP is indicative of functional unblinding and informative censoring (i.e., that early discontinuation of IP in subjects with elevated ALP is suggestive of informative censoring in the primary endpoint). The Applicant's use of "censoring" in this statement is applicable only if subjects were censored at the time of treatment discontinuation. However, subjects who discontinued treatment were not censored at the time of treatment discontinuation, and the analyses of efficacy endpoints included all events observed, regardless of treatment discontinuation. As shown in Table 10 and Table 26 in Section 8.3.4, on-study follow-up time was similar in the two arms in the USPI-labeled, USPI-contraindicated, and ITT populations (see Figure 3).

Table 10. Time On-Study and Time On-Treatment, ITT Population, Trial 747-302

Characteristic	OCA N=168	Placebo N=166
Time on treatment[1] (Months)		
Mean (SD)	29.5 (21.3)	25.1 (17.3)
Median (Q1, Q3)	27.1 (10.3, 49.2)	20.1 (12.0, 36.8)
Time on study[2] (Months)		
Mean (SD)	40.3 (20.3)	39.9 (19.2)
Median (Q1, Q3)	41.9 (23.4, 59.7)	40.9 (24.0, 58.0)

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt.

[1] Difference between treatment start date and treatment end date.

[2] Difference between randomization date and last contact date.

Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment arm; SD, standard deviation

4.2.5.3 Initiation of Commercial PBC Therapies

The Applicant stated that there was significant discontinuation of IP and crossover of subjects initially randomized to the placebo arm to commercial PBC therapies, and this resulted in a reduced likelihood of clinical outcome events in the placebo arm.

The Applicant prespecified methods to handle the intercurrent events of treatment discontinuation and initiation of commercial OCA in the SAP. Under the Applicant's prespecified primary estimand (i.e., an estimand using the treatment policy strategy to handle treatment discontinuation and initiation of commercial OCA), treatment discontinuation and initiation of commercial OCA cannot be sources of bias, because the treatment policy strategy means that the occurrence of clinical outcomes is considered to be of interest regardless of whether the intercurrent events occur.

Use of commercial OCA and concomitant medications in the ITT population is presented in Table 11. Per the protocol, subjects should have been discontinued from study drug if they initiated treatment with commercial OCA. There was more commercial OCA use in the placebo arm (16% in the ITT population) compared to the OCA arm (8% in the ITT population); however, the use of other concomitant medications was similar in the two arms. A similar trend was observed in the USPI-labeled population (Table 27 in Section 8.3.5).

Table 11. Use of Commercial OCA and Concomitant Medications, ITT Population, Trial 747-302

	OCA N=168			Placebo N=166		
Medication	**Newly Started**	**Dose Increased**	**Total**	**Newly Started**	**Dose Increased**	**Total**
Commercial OCA, n (%)	13 (7.7%)	-	13 (7.7%)	26 (15.7%)	-	26 (15.7%)
Concomitant medication, n (%)	24 (14.3%)	11 (6.5%)	35 (20.8%)	29 (17.5%)	8 (4.8%)	37 (22.3%)
UDCA	5 (3.0%)	9 (5.4%)	14 (8.3%)	7 (4.2%)	7 (4.2%)	14 (8.4%)
Fibrate	20 (11.9%)	2 (1.2%)	22 (13.1%)	21 (12.7%)	0 (0%)	21 (12.7%)
Oral budesonide	1 (0.6%)	0 (0%)	1 (0.6%)	2 (1.2%)	1 (0.6%)	3 (1.8%)

Source: Statistical reviewer using Applicant submitted dataset adsl2.xpt.
Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic

Notably, cross-over of subjects from the placebo arm to commercial OCA could potentially lead to results closer to the null of no treatment effect, because any events that occurred in subjects randomized to the placebo arm would be attributable to the placebo arm, regardless of use of commercial OCA. Despite this potential, which could hamper identification of a treatment effect, a trend towards harm of OCA was observed in the USPI-labeled population with respect to the endpoint of time to liver transplant or death with the confidence interval excluding 1 (Figure 4).

4.2.5.4 Differential Data Collection

To maximize data collection, the Applicant initiated biannual telephone follow-up with subjects who discontinued study treatment and consented to continue follow up in the study for the accrual of outcome and safety events. However, the Applicant stated that several components of the expanded primary endpoint were not collected or could have been under-reported in the biannual telephone follow-up because of the late timing of the expansion of the endpoint definition.

The Applicant stated that more subjects in the OCA arm continued clinic visits every 3 months, at which time all components of the expanded primary endpoint were collected, whereas more subjects in the placebo group were followed with biannual telephone assessments. The Applicant also states that telephone assessments could have been subject to recall and measurement bias, and as a result, the placebo group was impacted by measurement bias to a greater extent than the OCA group. Therefore, it is possible more events of the expanded primary endpoint were captured in the OCA arm compared to

the placebo arm due to this differential data collection. This may cause concern about the interpretation of the results for the expanded primary endpoint.

However, this indicates that the events in the primary endpoint definition prior to expansion and other key secondary endpoints were more accurately captured compared to those in the expanded primary endpoint definition. There is no trend of benefit observed on the more accurately captured primary endpoint prior to expansion or any other key secondary endpoints. Additionally, outcomes of liver transplant and death are the least likely to be impacted by any potential measurement and recall bias, and there are trends of harm on that endpoint.

4.3 Study 747-405: Real-World Data Study to Evaluate the Effectiveness of OCA on Hepatic Outcomes in PBC Patients (HEROES PBC; ClinicalTrials.gov Identifier: NCT05292872)

4.3.1 Introduction

The Applicant presents Study 747-405 as an adequate and well-controlled clinical investigation that verified the clinical benefit of OCA effectiveness for PBC. To assess this claim, the Review Team (a) completed a detailed analysis of the Study 747-405 methods and results; (b) assessed its RWD sources for relevance and reliability; and (c) assessed whether Study 747-405 meets the regulatory standards for an adequate and well-controlled clinical investigation.

Study 747-405 was a 67-month (June 2016 to December 2021) observational (nonrandomized) cohort study conducted in KOMODO, a U.S. electronic healthcare database that aggregates open and closed medical and pharmacy administrative claims from ≈150 U.S. health plans. Using Datavant, KOMODO accessed other data sources to determine (a), date of death (Social Security Death Index [SSDI] and Obituary Search); (b), results of laboratory tests (LabCorp and Quest Diagnostics); and (c), date of liver transplantation (Organ Procurement and Transplantation Network [OPTN]). Efficacy analyses specified a primary composite outcome with three components: (1) death; (2) liver transplantation; and (3) hepatic decompensation (variceal bleeding, ascites, or hepatic encephalopathy). See Table 36 and Figure 16 for tabular and graphical design summaries of Study 747-405. See Section 8.4.3 for the methods used to identify treatment-emergent adverse events of special interest (TEAESI).

Study 747-405 used healthcare claims and laboratory data to construct longitudinal patient histories and conceived each occurrence of abnormality in ALP (ALP >121 U/L) or TB (TB >1.2 mg/dL) as a decision point whereby a healthcare provider might prescribe or not prescribe OCA.

Study 747-405 determined eligibility by qualifying index dates with each index date classified as either treated or not treated with OCA. Each index date served as a start date (Time 0) for a period of follow-up.

A treated index date signified a patient's first pharmacy claim for OCA. To qualify as a treated index date, the patient's longitudinal history had to satisfy each of the following key inclusion criteria:

- PBC diagnostic criteria fulfilled (≥1 inpatient claim or ≥2 outpatient claims on different dates).
- Continuously covered by healthcare (closed claims) within 365 days before the index date.
- Age ≥18 years on the index date.
- ALP >121 IU/L or TB >1.2 mg/dL on the index date or during the preceding 365 days.

- Previous (on or after June 1, 2015) or concurrent treatment with UDCA (as determined by pharmacy claims).

Control index dates denoted the dates of ALP or TB abnormality in ≥18-year-old PBC patients with closed claims. Study 747-405 selected control index dates that fulfilled the criteria for UDCA treatment failure (inadequate UDCA response, UDCA intolerant, or UDCA discontinued):

4. Inadequate UDCA Response – ALP or TB above the upper limit of normal (ULN) with both (a) ≥270 days of UDCA treatment in the previous 365 days and (b) ≥60 days of UDCA treatment in the previous 90 days.
5. UDCA Intolerant – ALP or TB above the ULN >90 days after a single episode of UDCA treatment lasting ≤90 days.
6. UDCA Discontinued – ALP or TB above the ULN with ≥6-month lapse since completing the most recent treatment with UDCA.

Study 747-405 excluded treated and control index dates if screening criteria indicated a patient history of (a) non-PBC liver disease (e.g., hepatitis C), (b) other serious disease (e.g., cancer), or (c) hepatic decompensation (e.g., variceal bleed).

4.3.2 Study Design and Statistical Methods

Target Trial Emulation

The Applicant stated that Study 747-405 was designed to emulate a target randomized clinical trial (Hernán et al. 2008). Under this approach, the design of an analogous randomized clinical trial is formulated first (e.g., eligibility criteria, primary endpoint), and then this design is used as a guide to design the observational study. Each time point at which a patient meets the study inclusion criteria is referred to as an index date. Study 747-405 used the criteria described above to select OCA-treated and control index dates, with each index date serving as a start date (Time 0) for a period of follow-up. Study 747-405 included patients with (a) only one OCA-treated index date, (b) only control index dates (single or multiple), or (c) both an OCA-treated index date and one or more control index dates, as long as all control index dates preceded the OCA-treated index date.

Primary Analysis

An "index" refers to the follow-up period that starts at an index date. All analyses of Study 747-405 use indices rather than patients as the observation unit. As described above, a single patient may have contributed multiple indices to Study 747-405. The Applicant described the primary analysis in Study 747-405 as an as-treated approach, which they stated is analogous to using a while-on-treatment strategy with respect to the intercurrent event (i.e., postbaseline event) of switching away from the patient's initially used treatment (see the ICH E9R1 Guideline (November 2019)). An intercurrent event is defined as an event that occurs after an index, or follow-up time, has started and which either precludes the observation of the outcome variable or affects its measurement or interpretation (Gogtay et al. 2021). Under the as-treated analysis approach, indices are artificially censored when the patient deviates from their initial treatment, that is, events occurring after the switch are disregarded even if observed. Censoring is a form of missing data problem in which the time to event is not observed. The censoring rules in the primary as-treated analysis differed for indices in the OCA and control treatment arms as follows:

a. OCA-treated indexes were censored 90 days after OCA discontinuation or upon fibrate start, end to closed claims, or end of study period (December 31, 2021), whichever came first.

b. Control indexes were censored upon initiation of OCA, fibrate start, or UDCA reinitiation (for the subset of control periods qualified by UDCA discontinuation criteria), end to closed claims, or end of study period (December 31, 2021), whichever came first.

The CSR does not define the term *closed claims*. However, this term is a commonly used research term. One definition of closed claims is provided by Baser et al. (2023): "Closed-payer claims data refers to information from payers that can be provided directly by health insurance companies or a collection of employers sharing their employees' health claims with consulting services, revealing nearly all of a patient's healthcare activities within a fixed period of enrollment" and "With the enrollment file and eligibility information, the data also reveals when a patient does not visit the doctor or fill a prescription; therefore, adherence to treatment can be estimated."

As noted above, the statistical analysis followed a randomized trial emulation approach (Hernán et al. 2008; Danaei et al. 2013). The goal of the study design was to emulate a "sequence of hypothetical randomized trials" (CSR, p. 47). As a feature of this study design goal (e.g., Hernan et al., 2008; Danaei et al., 2011), rather than separately analyzing each hypothetical randomized trial and combining the results, the Applicant performed a single pooled analysis that included all indices contributed by participating patients. Under this design, a patient may have contributed multiple control indices, but only one OCA index. Because Study 747-405 included patients who contributed multiple indices to statistical analyses, the bootstrap was used to obtain valid standard errors and confidence intervals adjusted for within-patient correlated data.

As is common in observational studies, the OCA-treated indices and control indices differed in terms of baseline characteristics. Standardized morbidity ratio (SMR) weights were used to achieve balance on baseline confounders. SMR weights were used "to create a 'pseudo-population' of non-OCA-treated indices with the same covariate distribution as the OCA-treated patients at the time of OCA initiation" (Study 747-405 Protocol, pp. 30-31). Under this weighting approach, all the indices in the OCA cohort received an SMR weight of 1, and all the control indices received an SMR weight between 0 and 1. The weighted control cohort is intended to estimate what would have happened had patients who were treated with OCA instead not been treated with OCA.

SMR weights were computed from a logistic regression using the following confounders: pre- versus post-2020 coronavirus disease 2019 (COVID-19) pandemic; gender; age; blood levels of ALP, TB, ALT, AST, and platelet count (PLT); portal hypertension, cirrhosis; Charlson Comorbidity Index; whether on UDCA; time since first UDCA failure; and health insurance type. See Table 37 for more information on these confounders.

The primary treatment effect was estimated using an SMR-weighted Cox regression and bootstrap 95% confidence intervals for the time to first event of (a) death, (b) liver transplantation, or (c) hepatic decompensation, with the treatment indicator (OCA versus control) as the sole predictor. No statistical adjustment was made for possibly informative censoring.

Secondary and Sensitivity Analyses

Study 747-405 also assessed time to primary composite outcome under two alternative censoring rule sets, which the Applicant referred to as ITT-1 and ITT-2.

ITT-1 approach:

1. Control indices follow the same censoring rules as the primary analysis.
2. OCA indices were censored upon fibrate initiation, end to closed claims, or end of study period (December 31, 2021). OCA indices were not censored for OCA treatment discontinuation.

ITT-2 approach:

3. Control indices were not censored at OCA initiation or UDCA reinitiation. Control indices were censored upon fibrate initiation, end to closed claims, or end of study period.
4. OCA indices were censored upon fibrate initiation, end to closed claims, or end of study period. OCA indices were not censored for treatment discontinuation.

The ITT-1 and ITT-2 analyses were conducted by the Applicant in response to a request by the Agency dated November 2023, prior to the sNDA submission. The Agency recommended "sensitivity and exploratory analyses to describe the outcomes experienced by these patients after they met these censoring criteria" (refer to Section 3.2). These analyses approximated an ITT-like treatment effect and relaxed the censoring rules used in the primary as-treated analysis. However, these analyses had censoring rules inconsistent with ITT analysis, such as initiation of OCA in the ITT-1 analysis, and initiation of fibrates in the ITT-1 and ITT-2 analyses.

Additional Analyses Conducted by the FDA Review Team

The FDA review team identified two important concerns in the Applicant's analyses: (1) the composite endpoint includes events of hepatic decompensation, which in the discussion section below is shown to be subject to outcome misclassification; and (2) the Sponsor's as-treated analysis is likely affected by informative censoring, in which patients who experience adverse events or whose disease worsens are more likely to discontinue treatment.

To address these two limitations, the FDA review team conducted an ITT-like analysis of the two-point composite of time to death or liver transplantation. This analysis allowed no censoring for intercurrent events such as treatment switch, start of fibrates, or end to closed claims. Every patient index was considered from the time of study entry to either study completion (December 31, 2021) or an event. Note that because hepatic decompensation is not included in this new outcome composite, it is not necessary to censor at the end of the closed-claims period. Table 12 lists the censoring rules of the analyses. The FDA ITT analysis has the following two important advantages over the as-treated, ITT-1, and ITT-2 analyses of the three-point composite conducted by the Applicant:

- By focusing on the two-point composite of death and liver transplantation, the FDA analyses are not subject to the potential misclassification associated with the outcome of hepatic decompensation. As discussed below, death and liver transplantation outcomes might be regarded as more reliable endpoints than hepatic decompensation.
- The FDA's ITT analysis does not censor for intercurrent events and is therefore not likely to be affected by informative censoring. Because SSDI and OPTN capture deaths and liver transplantation events regardless of whether a patient is covered by a reporting insurance plan, the FDA ITT analysis of the two-point composite does not require censoring due to closed claims.

The most important limitation of ITT analyses is that they may include follow-up time past the expected end of clinical efficacy. However, without ITT, indices may be subject to informative censoring, resulting in a biased overall estimate.

Table 12. Study 747-405: Censoring Rules for Intercurrent Events by Type of Analysis

Criterion	Censoring Rule Set, by Analysis							
	Applicant's As-Treated (3-Point Composite)		Applicant's ITT-1 (3-Point Composite)		Applicant's ITT-2 (3-Point Composite)		FDA ITT[1] (2-Point Composite)	
	OCA	CNTL	OCA	CNTL	OCA	CNTL	OCA	CNTL
OCA end	✓							
OCA start		✓		✓				
Fibrate start	✓	✓	✓	✓	✓	✓		
UDCA restart		✓*		✓*				
Closed claims end	✓	✓	✓	✓	✓	✓		
Study end	✓	✓	✓	✓	✓	✓	✓	✓

Source: Generated by the FDA reviewer.

* Applicable to control periods identified by laboratory test abnormality that fulfilled UDCA discontinuation criteria

[1] FDA's ITT-like analyses of death and liver-transplant (two-point composite versus Applicant's three-point composite of death, liver transplantation, and hepatic decompensation events).

Abbreviations: OCA, obeticholic acid; CNTL, control; ITT, intent-to-treat; UDCA, ursodeoxycholic acid

4.3.3 Results

Baseline Characteristics

Study 747-405 identified 2,552 unique patients with (a) age ≥18 years, (b) ≥1 OCA dispensing during the enrollment period (June 1, 2016 to December 31, 2021), and (c) encounter claims that fulfilled the criteria for PBC. Section 8.4.1 summarizes the subsequent attrition, after which 432 patients with treatment exposure to OCA were eligible for the study.

Study 747-405 also identified 97,648 unique patients with encounter claims that fulfilled the criteria for PBC. Section 8.4.2 summarizes subsequent attrition, after which the control group comprised 4,535 unique patients—4,326 patients without a period of OCA-treated follow-up and 209 patients with a subsequent period of OCA-treated follow-up.

Efficacy analyses excluded 29 (6.7%) of the 432 OCA-exposed patients and 361 (8.0%) of the 4,535 control patients because of missing baseline data. Consequently, efficacy analyses assessed PBC outcomes in 403 OCA-treated patients (with each patient contributing only one follow-up period on OCA) and 4,174 control patients with 11,246 separately indexed follow-up periods not on OCA.

Table 13 lists selected baseline characteristics of (a) patients treated with OCA and (b) control periods before and after statistical weighting. Statistical weighting achieved acceptable control (absolute standardized mean difference <0.10) for most baseline covariates.

Table 13. Baseline Demographics and Clinical Characteristics, Patients Treated With Obeticholic Acid (OCA) and Control Periods Before and After Statistical Weighting, Study 747-405

	Treated With OCA N=403		Not Treated With OCA			
			Unweighted N=11,246		Weighted N=405.37	
Parameter	**n**	**%**	**n**	**%**	**n**	**%**
Enrollment period						
<2020	276	68.5	6,281	55.9	278.30	68.7
≥2020	127	31.5	4,965	44.1	127.07	31.3
Sex						
Female	369	91.6	10,146	90.2	369.47	91.1
Male	34	8.4	1,100	9.8	35.90	8.9
Age, years						
18-34	7	1.7	219	1.9	24.36	6.0
35-44	43	10.7	677	6.0	44.59	11.0
45-54	117	29.0	2,020	18.0	98.33	24.3
55-64	164	40.7	4,307	38.3	151.42	37.4
65-74	56	13.9	2,605	23.2	61.76	15.2
75-89	16	4.0	1,418	12.6	24.91	6.1
Cirrhosis						
Recorded	203	50.4	4,936	43.9	204.57	50.5
Not recorded	200	49.6	6,310	56.1	200.80	49.5
Portal hypertension						
Recorded	95	23.6	2,887	25.7	94.97	23.4
Not recorded	308	76.4	8,359	74.3	310.39	76.6
On UDCA at index						
Yes	292	72.5	7,236	64.3	294.57	72.7
No	111	27.5	4,010	35.7	110.80	27.3
UDCA failure type						
Inadequate	191	47.4	7,683	68.3	354.67	87.5
Discontinued	204	50.6	2,769	24.6	39.18	9.7
Intolerant	8	2.0	794	7.1	11.52	2.8
Total bilirubin (TB)						
≤1.2 mg/dL	329	81.6	9,434	83.9	332.66	82.1
>1.2 mg/dL	74	18.4	1,812	16.1	72.70	17.9
Alkaline phosphatase (ALP)						
28-138 U/L	23	5.7	2,835	25.2	36.28	8.9
139-166 U/L	33	8.2	2,839	25.2	50.91	12.6
167-224 U/L	96	23.8	2,884	25.6	83.56	20.6
225-1189 U/L	251	62.3	2,688	23.9	234.63	57.9
Alanine aminotransferase (ALT)						
3-29 U/L (<ULN)	127	31.5	6,272	55.8	140.80	34.7
30-89 U/L (1-2× ULN)	215	53.3	4,518	40.2	207.22	51.1
≥90 U/L (≥3× ULN)	61	15.1	456	4.1	57.34	14.1
Albumin (ALB)						
Missing	34	8.4	1,049	9.3	30.39	7.5
<3.8 mg/dL	37	9.2	1,481	13.2	53.97	13.3
≥3.8 mg/dL	332	82.4	8,716	77.5	321.01	79.2

Source: Epidemiology Review of Study 747-405.

Study 747-405 used ALP >121 U/L as an eligibility criterion.

Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal (1.2 mg/dL for TB and 30 U/L for ALT); N, number of observations in treatment arm; n, number of observations in specified population or group

Disposition and Baseline Characteristics

Table 14 summarizes outcome and censoring events for OCA indices and SMR-weighted control indices based on the Applicant's as-treated analysis. The proportion of indices censored due to end of closed claims in the primary as-treated analysis was similar in the two cohorts: 18.1% for OCA and 22.5% for control. However, the proportion of indices that were censored due to treatment switch was more than twice as high among OCA indices (53.3% total to 48.6% OCA end, 4.7% fibrate start) than control indices (21.1% total to 2.8% fibrate start, 12.3% OCA start, 6.0% UDCA restart).

Table 14. Outcome and Censoring Events for Primary Analysis, Patients Treated With Obeticholic Acid (OCA) and Control Periods After Statistical Weighting, Study 747-405

	Treated With OCA N=403		Not Treated With OCA (Weighted) N=405.37	
Event	**n**	**%**	**N**	**%**
Treatment outcome				
Death	2	0.5	7.23	1.8
Liver transplantation	0	0	1.57	0.4
Hepatic decompensation	6	1.5	23.03	5.7
Censored for				
Treatment switch	215	53.3	85.37	21.1
OCA end	196	48.6	N/A	
Fibrate start	19	4.7	11.18	2.8
OCA start	N/A		50.03	12.3
UDCA restart	N/A		24.16	6.0
Closed claims end	73	18.1	91.27	22.5
Study end	107	26.6	196.9	48.6

Source: CSR Table 14.2.1 (pp. 337-338).

Abbreviations: N/A, not applicable; N, number of observations in treatment arm; n, number of observations in specified population or group

The primary analysis followed: (a) 403 OCA-treated patients for a mean of 436 days, median of 282 days, interquartile range (IQR) of 148 to 586 days, and maximum of 1,929 days; and (b) 405.37 control periods (weighted) for a mean of 627 days, median of 476 days, IQR of 170 to 992 days, and maximum of 2,041 days. Table 15 lists the follow-up durations for the ITT-1 and ITT-2 conditions.

Table 15. Duration of Follow-up (in Days), by Method, for Patients Treated With Obeticholic Acid (OCA) and Control Periods After Statistical Weighting, Study 747-405.

	Treated With OCA N=403			Not Treated With OCA N=405.37 (Weighted)		
Method	**Mean**	**Median (IQR)**	**Max**	**Mean**	**Median (IQR)**	**Max**
PEP	436.2	282 (148-586)	1,929	627.1	476 (170-992)	2,041
ITT-1	723.4	621 (267-1,066)	2,010	627.1	476 (170-992)	2,041
ITT-2	723.4	621 (267-1,066)	2,010	738.1	639 (270-1,151)	2,041

Source: Epidemiology Review of Study 747-405.

Abbreviations: N, number of observations in treatment arm; PEP, primary endpoint analysis; ITT, intention to treat; IQR, interquartile range

Efficacy

Table 16 lists selected efficacy results for the primary as-treated analysis, as well as the Applicant's secondary ITT-1 and ITT-2 analyses of the primary composite of hepatic decompensation, liver transplant, or death.

Table 16. Selected Efficacy Outcomes, Patients Treated With Obeticholic Acid (OCA) and Control Periods After Statistical Weighting, Study 747-405

Outcome/ Analysis Method	Treated With OCA N=403		Not Treated With OCA N=405.37 (Weighted)		Treatment Effect	
	n	IR	N	IR	HR	95% CI
Primary composite						
As-treated	8	1.66	31.83	4.57	0.37	0.14-0.75
ITT-1	22	2.76	31.83	4.57	0.59	0.34-0.99
ITT-2	22	2.76	34.97	4.28	0.64	0.38-1.05

Source: CSR and Epidemiology Review of Study 747-405.

ITT-1: OCA-treated follow-up not censored for OCA end date.

ITT-2: OCA-treated follow-up not censored for OCA end date and OCA-untreated follow-up not censored for OCA start or UDCA restart.

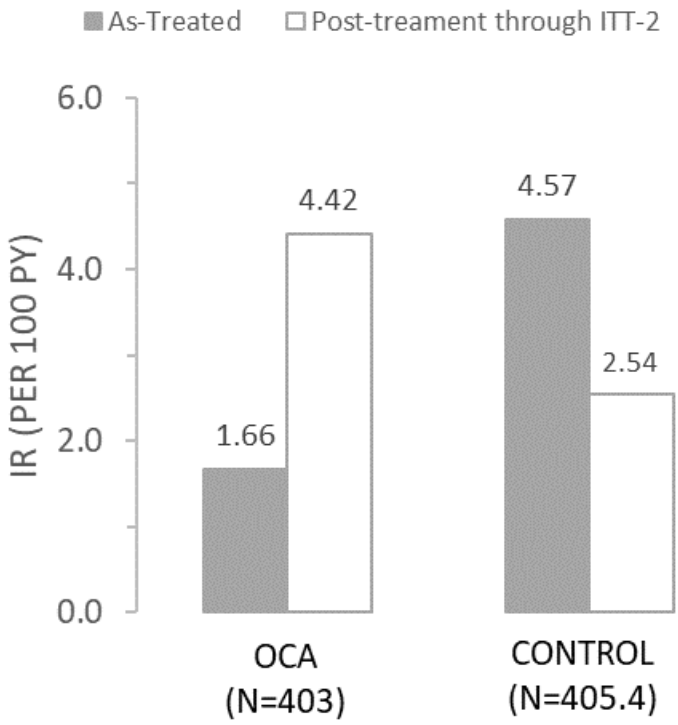
Abbreviations: N, number of observations in treatment arm; n, number with outcome; IR, incidence rate (per 100 patient-years); HR, hazard ratio; CI, confidence interval; ITT, intention to treat

During the primary as-treated analysis, eight primary events were observed among 403 OCA indices (IR 1.66 per 100 PY) and 31.83 primary events (weighted) were observed among 405.37 control indices (IR 4.57 per 100 PY). ITT-2 analyses followed patient indices for longer after censoring compared to the as-treated analysis. Figure 10 shows the observed event rate for the primary composite outcome of hepatic decompensation, liver transplantation, or death during the as-treated follow-up and during the period after censoring from the as-treated analysis but prior to censoring in the ITT-2 analysis conducted by the Applicant.

Among the indices for patients in the OCA group, the observed IR was 1.66 per 100 PY during the as-treated period, compared to a 2.7-fold increase post-treatment of 4.42 per 100 PY. Among the indices for control patients, the observed IR was 4.57 per 100 PY during the as-treated period, compared to a 44% decrease post-treatment of 2.54 per 100 PY. This pattern of incidence rates is consistent with at least two possible explanations: (1) OCA is associated with a beneficial treatment effect that disappears after treatment discontinuation, or (2) the 53.3% of patients who switched from OCA had a different risk profile than those who stayed on-treatment, and part of the estimated treatment effect in the as-treated analysis is caused by differences in cohorts due to this differential treatment discontinuation. Because of the absence of accurate and complete data at the time of treatment switch, it is not possible to conduct analyses to distinguish these two scenarios.

Together, these observations describe a setting with a high potential for informative censoring in the as-treated analysis. ITT analyses include follow-up and events observed after treatment discontinuation and therefore are unlikely to be affected by informative censoring.

Figure 10. Primary Composite Outcome, Incidence Rate (IR) per 100 Patient-Years (PY) for (a) OCA-Treated Patients and (b) Control Periods, During (Primary) As-Treated Follow-Up and From the End of As-Treated Follow-Up Through the End of the ITT-2 Follow-Up



Source: Epidemiology Review of Study 747-405.
Patient counts and incidence rates after Standardized Morbidity Ratio (SMR) weighting are shown.
Abbreviations: ITT, intent-to-treat; OCA, obeticholic acid

Additional Analyses Conducted by the FDA Review Team

On May 1, 2024, the Applicant informed the FDA that an inspection found that 58 (1.2%) of the 4,758 patients should not have been included in the eligible population. In a response to an information request, the Applicant submitted a list of these 58 patients to the FDA on May 13, 2024. We note that all results and tables for Study 747-405 in this document prior to this section are based on the original data that include these 58 patients. The FDA confirmed that this issue affected approximately 1.2% of study patients and did not meaningfully impact the results of the primary analysis. This section discusses the results of additional analyses conducted by the FDA Review Team. These additional analyses use updated data, which exclude the data of the 58 patients.

As discussed above, the FDA review team identified two limitations in the Applicant's analyses: (1) possible misclassification of hepatic decompensations, and (2) possible informative censoring. To address these issues, the FDA review team conducted an ITT-like analysis of the two-point composite of time to death or liver transplantation that allowed no censoring for intercurrent events. For completeness, this section also presents the results of as-treated, ITT-1, and ITT-2 analyses of the two-point composite of time to death or liver transplantation, to enable comparison with the Applicant's analyses of the three-point composite.

Table 17. Analyses of Time to Liver Transplantation or Death, Patients Treated With Obeticholic Acid (OCA) and Control Periods After Statistical Weighting, Study 747-405

Outcome/ Analysis	Treated With OCA N=402			Not Treated With OCA N=404.55 (Weighted)			Treatment Effect	
Method	n	PY	IR	n	PY	IR	HR	95% CI
As-treated	2	482.8	0.41	11.97	715.55	1.67	0.27	0.00-0.93
ITT-1	13	814.2	1.6	11.97	715.55	1.67	0.92	0.43-1.86
ITT-2	13	814.2	1.6	12.72	848.8	1.5	1.07	0.49-2.07
FDA ITT	19	1157.6	1.64	22.09	1127.1	1.96	0.80	0.45-1.38

Source: FDA Review Team.

Abbreviations: IR, incidence rate per 100 PY; PY, patient-years; HR, hazard ratio; CI, confidence interval

Table 17 shows the results of analyses of the two-component composite of time to liver transplantation or death. As-treated analyses for this endpoint observed 2 events in the OCA cohort and 11.97 (weighted) events in the control cohort. Using the Applicant's approach, the as-treated estimate of the HR for the two-component endpoint is 0.27 with a 95% CI of 0.00, 0.93, which excludes the value of 1, as is the case for the three-component endpoint. Analysis of this two-component endpoint using similar censoring rules as the Applicant's ITT-1 and ITT-2 analyses for the three-point composite yielded hazard ratios of 0.92 (0.43, 1,86) and 1.07 (0.49, 2.07).

Table 17 also shows results of the FDA's ITT analysis. Relative to the as-treated analysis, the FDA's ITT analysis yielded 17 additional events (19 total) in the OCA cohort and 10.12 additional events (22.09 total) in the control cohort. The estimated hazard ratio for the time to liver transplantation or death based on the FDA's ITT analysis was 0.80 with a 95% CI of 0.45, 1.38. The estimates for the ITT-1, ITT-2, and the FDA's ITT analysis are closer to the null value of 1 than the as-treated analysis, and the respective confidence intervals span the value of 1.

The as-treated and ITT analyses have different limitations. The as-treated analyses in Study 747-405 are challenging to interpret due to the different lengths of follow-up in the two cohorts and the high potential for informative censoring. In this study, the FDA ITT analysis of liver transplantation or death requires no censoring other than study completion on December 31, 2021, and therefore it is unlikely to be affected by missing data or informative censoring. However, in real-world studies with short treatment durations, an ITT analysis may include follow-up time past the expected end of clinical efficacy. The Applicant's ITT-1 and ITT-2 analyses have elements of both the as-treated and the FDA ITT analyses, and as such they have some of the strengths and limitations of both analysis strategies.

Treatment-Emergent Adverse Events

Table 18 summarizes TEAESI counts and incidence rates during periods of treatment or not with OCA. Study 747-405 reported the TEAESI of pruritus with a weighted incidence of 7.9 versus 6.4 per 100 PYs during follow-up periods of treatment or not with OCA. No other TEAESI had a higher incidence during the OCA treatment than the OCA nontreatment period.

Table 18. Treatment-Emergent Adverse Event of Special Interest (TEASI), Number (n) and Incidence Rate (IR, per 100 Patient-Years), During Periods Treated and Not Treated With Obeticholic Acid (OCA), Study 747-405

Treatment-Emergent Adverse Event of Special Interest (TEAESI)	Treated With OCA N=403, PY 562.6		Not Treated With OCA N=405.4, 780.3 PY (Weighted)	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Hepatic	164 (40.7)	49.5 (41.5, 59.2)	208.4 (51.4)	54.4 (49.1, 60.3)
Dyslipidemia	69 (17.1)	14.8 (11.6, 18.9)	97.3 (24.0)	16.3 (13.8, 19.2)
Cholecystitis/cholelithiasis	54 (13.4)	10.9 (8.3, 14.4)	82.5 (20.4)	13.0 (10.5, 16.0)
Renal	45 (11.2)	8.9 (6.6, 12.0)	85.6 (21.1)	13.4 (11.2, 15.9)
Pruritus	41 (10.2)	7.9 (5.7, 10.9)	44.9 (11.1)	6.4 (4.8, 8.5)
Cardiovascular	37 (9.2)	7.0 (5.0, 9.7)	52.8 (13.0)	7.5 (6.3, 9.1)

Source: Study 747-405, Table 70.

Patient-years accumulated before event or end of safety follow, (a) OCA-treated: 331.0, 466.2, 493.4, 507.0, 518.0, and 529.9 patient-years and (b) OCA-untreated: 383.1, 597.5, 635.3, 639.0, 703.8, and 699.5 patient-years for TEAESIs of Hepatic, Dyslipidemia, Cholecystitis/Cholelithiasis, Renal, Pruritus, and Cardiovascular, respectively.

Abbreviations: IR, incidence rate; PY, patient-years

4.3.4 Discussion

Introduction

The Applicant presents results from Study 747-405 as principal source of support for traditional approval (clinical benefit confirmed) following accelerated (Subpart H) approval. This approach obligates study methods that use highly reliable strategies to produce clinically germane results with high confidence.

Study 747-405 used administrative claims and linked datasets to define key data elements that included (a) diagnosis of PBC, (b) UDCA failure, (c) treatment with OCA, and (d) clinical outcomes of interest (death, liver transplantation, and hepatic decompensation). Certain clinically relevant data elements were not available. Examples included (a) anti-mitochondrial antibody (AMA) or PBC-specific antibody titer, (b) liver biopsy results, (c) measures of liver stiffness, and (d) reasons for OCA discontinuation.

PBC Diagnosis, Treatment Group Assignment, and Patient Follow-up

A clinical diagnosis of definite or probable PBC requires at least two of the following three conditions: (a) ALP elevated for ≥6 months, (b) elevated AMA or PBC-specific antibody titer, and (c) consistent histology on liver biopsy. Functionally, Study 747-405 developed a proxy for a clinical diagnosis of PBC by restricting index dates to patients with (a) ≥1 inpatient or ≥2 outpatient pre- or post-index encounters with diagnostic coding for PBC (ICD-9 571.6 or ICD-10 K74.3), (b) cholestatic laboratory abnormality (elevated ALP or TB) measured on the index date or during the previous 365 days, (c) pre-index pharmacy dispensing for UDCA (a medication commonly used to treat PBC but also other cholestatic conditions), and (d) no pre-index medical encounters with diagnostic coding for a non-PBC cholestatic condition (e.g., primary sclerosing cholangitis). This algorithm identified PBC with unknown accuracy (false positivity).

An analyzed population that includes patients with conditions other than PBC produces effect estimates less relevant to the patient population indicated by FDA labeling. Lack of comparability between the two arms might occur if misclassification of PBC (a) occurs more frequently in one comparison group (OCA-treated or OCA-untreated) and (b) describes patients with different underlying expectations (risks) for an unfavorable treatment outcome (death, liver transplantation, or hepatic decompensation event), leading to confounding or selection bias (due to informative censoring or some other reason). This pattern seems plausible because Study 747-405 used filled OCA prescriptions to classify follow-up time as treated with OCA or not treated with OCA. After the labeling revisions in May 2021 (Boxed Warning

added), for example, the fact of OCA prescription itself possibly captured prescriber confidence in PBC diagnosis and hepatic status as suited for OCA (i.e., good prognosis patient without decompensated cirrhosis, prior decompensation event, or cirrhosis with portal hypertension).

Study 747-405 used statistical methods to achieve baseline comparability between treated and control with respect to certain measured covariates. However, the adequacy of statistical adjustment requires high confidence in the (a) accuracy of the information used to exclude patients with explanations for abnormal ALP or TB other than PBC and (b) ability of certain covariates to capture differences in prognosis fully and accurately. Furthermore, baseline comparability does not necessarily assure comparability during follow-up if certain factors determine both a change in treatment and subsequent risk for an outcome event of interest.

Using pharmacy claims, Study 747-405 defined a period of treatment as days of treatment supplied by a sequence of OCA dispensings. The method permitted gaps between dispensings up to 90 days in duration and added 90 days to the last dispensing in sequence. A 90-day extension might or might not adequately capture drug-related benefits expected to emerge after start of treatment (latent outcomes) or persist after treatment discontinuation. This uncertainty complicates interpretation of the results of the primary (as-treated) analysis.

Linking Claims to Other Data Sources

The reliability of death and liver transplantation outcomes for Study 747 405 depends on the accuracy of Datavant's privacy-preserving record linkage (PPRL) methodology.

Publicly available validation studies (Bernstam et al. 2022; Leidos Biomedical Research 2023) indicate that the accuracy of Datavant PPRL depends on the (a) quality (accuracy and completeness) of personally identifiable information (PII) in source data, (b) elements of PII used to create patient tokens, and (c) matching algorithms used to link records.

Documents submitted by the Applicant use vague language to describe the Datavant tokens and algorithms used by Study 747-405 to match patient records across data sources. The Review Team lacked (a) clarity regarding the Datavant tokens and algorithms used in Study 747-405, (b) specific information about the quality of the underlying PII in KOMODO, and (c) results of the validation studies conducted in the PBC patient population assembled for Study 747-405.

Hepatic Decompensation Outcomes

Study 747-405 used healthcare claims to identify hepatic decompensation events. Hepatic decompensation events were not adjudicated, verified, or validated against secondary sources of information, such as, primary medical records.

Unlike death and liver transplantation, hepatic decompensation (variceal bleed, hepatic encephalopathy, or ascites) entails clinical concepts with subjective elements. Trial 747-302, for instance, qualified hepatic encephalopathy as an outcome by specifically requiring (a) new onset or recurrence, (b) hospitalization ≥24 h, and (c) grade ≥2 severity (according to the West Haven criteria). Trial 747-302 actively ascertained occurrences of hepatic encephalopathy (and other liver-related outcomes) with documentation (a) on an electronic case report form (eCRF) signed by a clinical investigator and (b) final outcome event adjudicated by an independent Hepatic Outcomes Committee (HOC).

By comparison, Study 747-405 identified hepatic encephalopathy by hospital insurance claim that listed (in any priority position) one of 13 diagnosis codes, such as, ICD-10 G93.40 (Encephalopathy, unspecified). In addition to coding error and misdiagnosis, the appearance of one of these 13 codes on a hospital insurance claim might indicate (a) an incident hepatic encephalopathy event, (b) workup to rule-out hepatic encephalopathy, or (c) a history of hepatic encephalopathy.

Validation studies reported in the medical literature indicate that certain diagnosis codes when used in specific settings might identify hepatic decompensation events with modest accuracy (e.g., 70% to 90% positive prediction) (Lo Re et al. 2011; Goldberg et al. 2012; Kanwal et al. 2012; Lapointe-Shaw et al. 2018; Mapakshi et al. 2018; Bengtsson et al. 2020; Hayward et al. 2020). The accuracy of diagnosis codes or code combinations might vary by data source and study context. Producing substantial evidence of effectiveness creates an expectation of sensitive and specific methods for determining treatment outcomes. The expected level of accuracy might require a two-stage approach that first uses a sensitive code-based algorithm to screen for potential cases with the presence or absence of a treatment outcome subsequently confirmed by clinical review of primary medical records. By comparison, Study 747-405 identified hepatic decompensation events by means of a single-stage method that relied on a set of diagnostic codes of uncertain sensitivity and specificity. Misclassification of the hepatic decompensation outcome presents a major threat to the validity of the results of Study 747-405.

Outcome misclassification, if nondifferential with respect to exposure, might be expected to attenuate quantitative estimates of a causal association between a drug treatment and a medical outcome (i.e., bias toward the null). Regarding nondifferential misclassification as questionable, FDA conducted a quantitative bias analysis (QBA) (see Section 8.4.4), which identified plausible scenarios whereby differential outcome misclassification might explain a substantial portion of the treatment benefit observed in Study 747-405.

Primary As-Treated Analysis

The primary as-treated analysis conducted by the Applicant compared the time to first event for the composite of hepatic decompensation, liver transplantation, or death. This analysis estimated a hazard ratio associated with OCA of 0.37 with a 95% CI of 0.14, 0.75. The FDA review team identified two important limitations in this analysis: (1) possible misclassification of hepatic decompensations, and (2) possible informative censoring. To address these issues, the FDA review team conducted an ITT-like analysis of the two-point composite of time to death or liver transplantation that allowed no censoring for intercurrent events. The estimated hazard ratio for this analysis was 0.80 with a 95% CI of 0.45, 1.38. The ITT-1, ITT-2, and FDA's ITT analyses of the two-point composite of time to liver transplant or death did not confirm the clinical efficacy of OCA. The main limitation of ITT analyses in observational studies is that they may include follow-up time beyond clinical efficacy.

4.4 Summary of the Ocaliva Program for PBC

4.4.1 Summary of Efficacy for Trial 747-302

The randomized, controlled clinical trial, Trial 747-302, failed to demonstrate efficacy on the primary endpoint (HR=0.84, 95% CI: 0.61, 1.16 for the ITT population with a p-value of 0.304) and indicates harm regarding liver transplant/death (HR=1.18, 95% CI: 0.72, 1.93 for the ITT population and HR=4.77, 95% CI: 1.03, 22.09 for the USPI-labeled population). The liver transplant/death results in the USPI-labeled

population were in the direction of harm, despite placebo subjects' use of commercially available OCA hampering the detection of this signal of harm.

Therefore, the Agency does not consider that clinical benefit has been verified by Trial 747-302 and conversely that there is suggestive evidence of harm.

4.4.2 Summary of Safety for Trial 747-302

OCA induced hepatobiliary toxicity mimics progression of underlying PBC. Therefore, a comparison of the OCA and placebo groups in Trial 747-302 offers evidence of an association of OCA use with hepatotoxicity. In the USPI-labeled population, 11 OCA subjects died or had a liver transplant versus 2 placebo subjects, resulting in OCA-exposed subjects having a lower estimated probability of surviving without liver transplant compared to those who received placebo.

In the USPI-labeled population, five of the seven subjects in the OCA-treatment arm requiring liver transplantation did not have cirrhosis at baseline. One subject in the placebo arm who required liver transplantation began commercial OCA following the discontinuation of placebo treatment. Based on the natural history of PBC, the tempo of a PBC patient noncirrhotic at baseline, it would not be expected that six of eight subjects in Trial 747-302 would progress to requiring liver transplantation due to the development of end-stage liver disease.

In the USPI-labeled population, possible DILI occurred in 4.9% of the OCA-treated subjects compared to 1.5% of the placebo-treated subjects. DILI was dose-dependent (subjects with advanced cirrhosis) and dose-independent (subjects with early-stage disease); moreover, the DILI signature was associated with hepatocellular, cholestatic, or mixed injury.

New onset or worsening of pruritus is a key adverse reaction. Pruritus led to treatment interruption and discontinuation, and was an indication for liver transplantation.

4.4.3 Summary for Study 747-405

Study 747-405 was an observational cohort study designed to compare PBC patients treated or not with OCA in terms of the risk of a primary composite endpoint of death, liver transplant, or hepatic decompensation. Study 747-405 used healthcare claims data, laboratory data, SSDI, and OPTN to identify patients with PBC who met the inclusion/exclusion criteria, exposure, and outcome, and conducted statistical analyses to compare patients treated with to those not treated with OCA.

After a careful assessment, the Agency reached a preliminary conclusion that Study 747-405 does not meet the regulatory standards for an adequate and well-controlled clinical investigation. Study 747-405 used methods with unknown or uncertain reliability when (a) defining PBC with poor response to UDCA, (b) linking claims to external data sources, (c) identifying hepatic decompensation events, and (d) defining a follow-up period to adequately capture outcomes of interest. As summarized below, Study 747-405 also failed to use appropriate methods to address potential informative censoring. After accounting for plausible effects of erroneous data or improper design or analysis, the Agency has considerable doubt regarding the comparability of the OCA-treated and control conditions both at baseline and during follow-up.

The primary statistical analysis conducted by the Applicant estimated a hazard ratio of 0.37 with a 95% CI of 0.14, 0.75 for the primary endpoint based on an as-treated strategy that was found to be not appropriate in this study. The Review Team concluded that this analysis may be susceptible to informative censoring and misclassification of hepatic decompensation events. To address these

limitations, the FDA conducted an ITT-like analysis of a composite endpoint of death or liver transplant, and obtained an estimated HR of 0.80 with a 95% CI of 0.45, 1.38. ITT analyses have limitations, such as the potential to include follow-up time beyond the expected end of a product's clinical efficacy.

Study 747-405 did not meet the standards for an adequate and well-controlled investigation. The analyses conducted by the Applicant and the FDA to estimate a clinically and statistically interpretable endpoint have different limitations. Together, they indicate that the study does not verify the clinical benefit of OCA.

5 Summary of Issues for the AC

5.1 Key Issues

1. The analysis of the primary endpoint in Trial 747-302 does not demonstrate the benefit of OCA in either the ITT population or in subjects who reflect the indicated population in the current labeling (i.e., the USPI-labeled population).
2. Trial 747-302 showed harm with excess liver transplantation and death in OCA-treated USPI-labeled subjects.
    - The design of Study 747-405 has important limitations that affect the interpretability of the results.
    - The Applicant's as-treated analysis for the composite of hepatic decompensation, liver transplant, or death in Study 747-405 estimated an HR for OCA of 0.37 with a 95% CI of 0.14, 0.75). The Review Team considered this analysis difficult to interpret because of possible misclassification of hepatic decompensations and the potential for informative censoring.
    - For Study 747-405, the Agency conducted ITT analyses of liver transplant or death to address the potential deficiencies in the as-treated analysis. The FDA's ITT analysis estimated a hazard ratio of 0.80 with a 95% CI of 0.45, 1.38 and failed to confirm clinical benefit. The ITT analyses may be limited by the inclusion of follow-up time beyond the period of clinical efficacy.

6 Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This predecisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	Primary biliary cholangitis (PBC) is a rare autoimmune chronic liver disease characterized by intrahepatic bile duct injury/destruction and progressive impairment of bile flow in the liver. Liver injury occurs due to inflammation as well as bile stasis. Generally, PBC presents clinically in the fifth or sixth decade of life. Younger patients (35 to 50 years of age) may experience a more aggressive disease course. – Female to male ratio is 9:1. – Low bone mass is another extrahepatic concern, mainly in patients with advanced PBC. Patients with PBC can have other autoimmune conditions such as Hashimoto thyroiditis, CREST syndrome, Sjogren syndrome, rheumatoid arthritis, telangiectasias, systemic sclerosis, and celiac disease. – Osteoporosis, renal tubular acidosis, various skin conditions (lichen planus, discoid lupus, pemphigoid), and sicca syndrome (dry eyes/mouth) are also commonly associated with primary biliary cirrhosis. Cholestasis also affects lipid metabolism. Hyperlipidemia is present in about 85% patients.	PBC is a rare cholestatic autoimmune liver disease with negative impacts on quality of life and longevity. –PBC progresses at varying rates, with some patients experiencing liver decompensation over years and others over decades. – Fibrosis and cirrhosis are major predictors of poor outcome. – Pruritus (70%) and fatigue (80%) are two common and sometimes disabling symptoms.
Current Treatment Options	Ursodeoxycholic acid (UDCA) was approved for treatment of PBC by FDA in December 1997. The recommended dose is 13 to 15 mg/kg per day. About 60% of patients achieve a biochemical treatment response associated with expected survival similar to the general population (Marschall et al. 2019). Drugs approved under the accelerated approval pathway using ALP and TB as surrogate endpoints for treatment of patients with PBC who have inadequate response to UDCA or are intolerant to UDCA as a monotherapy, include: 1. Obeticholic acid (OCA) 2. Iqrivo (elafibranor) 3. Livdelzi (seladelpar)	About 40% of patients achieve a partial or no biochemical response to UDCA. These patients are at risk of liver-related complications leading liver transplantation and death. Patients with cirrhosis generally do not respond to UDCA and do not achieve the benefit of improved survival associated with its use. OCA cannot be used in patients with compensated cirrhosis with portal hypertension or in patients who have had a liver decompensation event.

	Evidence and Uncertainties	Comments to the Advisory Committee
	• Fibrates are used off-label for the treatment of PBC.	In 2024, elafibranor and seladelpar were approved for treatment of PBC under the accelerated approval pathway, and the clinical benefit of treatment is unknown. There remains an unmet need for additional treatments for PBC, especially for patients who do not respond to, or who are unable, to take currently available therapies.
Benefits	**Trial 302** This randomized, controlled clinical trial failed to demonstrate efficacy on the primary endpoint (hazard ratio of 0.84 [95% CI: 0.61, 1.16] for the ITT population with the associated p-value of 0.304). Data showed potential harm on liver transplant/death (hazard ratio of 1.18 [95% CI: 0.72, 1.93] for the ITT population and 4.77 [95% CI: 1.03, 22.09] for the USPI-labeled population). **Study 405** This nonrandomized observational study showed the following results: (a) the As-Treated efficacy on a primary composite outcome with a hazard ratio of 0.37 [95% CI: 0.14, 0.75] and (b) the FDA estimated ITT-like efficacy for a composite outcome of death or liver transplantation with a hazard ratio of 0.80 [95% CI: 0.45, 1.38].	**Trial 302** The Applicant asserted that Trial 302 was uninterpretable. However, the Agency considers that Trial 302 provides interpretable and informative results regarding the benefit-risk balance of OCA. In the USPI-labeled population, there is a signal of harm based on the clinical outcomes of liver transplantation and death. **Study 405** The Agency reached a preliminary conclusion that Study 747-405 did not meet regulatory standards for an adequate and well-controlled clinical investigation because of uncertainty about (a) definition of PBC with poor response to UDCA, (b) links between claims and external data sources, (c) hepatic decompensation outcomes, and (d) statistical methods. Results from the as-treated analysis are difficult to interpret because of treated versus control group differences in lengths of follow-up and potential for informative censoring. Results from the FDA ITT-like analysis are not affected by informative censoring. However, ITT analyses might include follow-up time past the expected end of clinical efficacy.
Risks and Risk Management	In the USPI-labeled population - Liver transplant and deaths (11 in OCA arm versus 2 in placebo arm) Incidence of DILI (3 in OCA arm versus 1 in placebo arm) Pruritus leading to treatment interruption, requirement of additional therapies for alleviating pruritus, treatment discontinuation, and liver transplantation occurred in higher	Clinical and biochemical markers were not predictive of poor outcomes, i.e., OCA cannot be discontinued in timely manner. This underscores the unpredictable nature of hepatotoxicity due to OCA.

	Evidence and Uncertainties	Comments to the Advisory Committee
	number of OCA treated subjects compared to placebo-treated subjects	Risk mitigation for these adverse outcomes is not feasible in any subpopulation.

Table 19. Key Benefits and Risks

Effects Table of Key Benefits and Risks - Clinical Trial 747-302/401				
Endpoint	**Definition**	**ITT Population OCA (N=168) vs. Placebo (N=166) HR (95% CI)**	**USPI-Labeled Population OCA (N=81) vs. Placebo (N=68) HR (95% CI)**	**Notes & Uncertainties**
Benefits (Favorable Effects)				
FDA expanded endpoint (prespecified primary endpoint)	Time from randomization to the first occurrence of: Death (all-cause) Liver transplant Hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, bacterial empyema Uncontrolled or refractory ascites requiring large volume paracentesis Portal hypertension syndromes MELD-NA score ≥ 15 for subjects with baseline MELD-NA score <12 MELD score ≥ 15 for subjects with baseline MELD-NA score ≥ 12 Progression to decompensated liver disease Progression to clinical evidence of portal hypertension without decompensation	0.84 (0.61, 1.16)	0.88 (0.47, 1.65)	- Results are not statistically significant -The primary endpoint was revised later in the trial. (Discussion started September 2021) -Includes some events that are based on biomarkers. -Applicant states that events might not be captured reliably for all subjects due to the late change in the primary endpoint.

Effects Table of Key Benefits and Risks - Clinical Trial 747-302/401				
FDA primary endpoint prior to the revision	Time from randomization to the first occurrence of: Death (all-cause) Liver transplant Hospitalization for new onset or recurrence of; variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis Uncontrolled ascites MELD score ≥15	1.01 (0.68, 1.51)	1.53 (0.59, 3.97)	-Point estimate for USPI-labeled population in the direction of harm
Death & Liver Transplant	Time to liver transplant or death (all-cause)	1.18 (0.72, 1.93)	4.77 (1.03, 22.09)	-Direction of harm for OCA (nominal p-value 0.029 for UPSI-labeled population)

Outcome	Definition	OCA vs. Placebo (Number of patients (%))	Notes & Uncertainties
	Harms/Risks		
Death (ITT Population)	Deaths that occurred due to any cause during the trial.	OCA n=16 (9.5%) Placebo n=12 (7.2%)	
Death (USPI-labeled population)	USPI labeled population (*which is currently the population in which labeling allows use of OCA).	OCA n=4 (4.9%) Placebo n=1 (1.5%)	Based on the natural history of PBC, noncirrhotic subjects were not expected to progress to liver transplant or death.
Liver Transplant (ITT population)	Liver transplantation that occurred in the safety population during the trial.	OCA n=20 (11.9%) Placebo n=18 (10.8%)	
Liver Transplant (USPI-labeled population)	Liver transplantation that occurred in the USPI-labeled population during the trial.	OCA n=7, (8.6%) Placebo n=1 (1.5%), liver transplantation occurred two years after the subject switched to commercial OCA	Based on the natural history of PBC, noncirrhotic subjects were not expected to progress to liver transplant or death.

Effects Table of Key Benefits and Risks - Clinical Trial 747-302/401		
DILI (USPI-labeled population)	These assessments were based on biochemical tests. The definition of DILI did not encompass death and liver transplant.	OCA=3 (3.7%) Placebo=1 (1.5%)
Pruritus (USPI-Labeled population)	Overall incidence of new-onset or worsening of pruritus	OCA=67 (82.7%) Placebo=33 (48.5%)
	Pruritus leading to drug discontinuation	OCA=12 (14.8%) Placebo=2 (2.9%)

Effects Table of Key Benefits and Risks - RWE Study 747-405			
Outcome	**Definition**	**Treated vs. Untreated HR (95% CI)**	**Notes & Uncertainties**
		Benefits (Favorable Effects)	
Primary Composite	Time to death (any cause), liver transplantation, or hepatic decompensation event (hospitalization for variceal bleed, ascites, or hepatic encephalopathy)	As-treated[1]: 0.37 (0.14-0.75) ITT2[2]: 0.64 (0.38-1.05)	- Nonrandomized study design - Disease (PBC) not assured - Comparability not assured by the study design - Hepatic decompensation events not validated - Benefit estimate contingent on not fully validated outcome and questionable analytic method - As-treated method susceptible to postrandomization confounding, informative censoring, and selection bias - Clinical benefit not shown by FDA-ITT analysis of time to death (any cause) or liver transplantation
Exploratory Ad Hoc	Time to death (any cause) or liver transplantation	As-treated[1]: 0.27 (0.00-0.93) FDA ITT[3]: 0.80 (0.45-1.38)	
Outcome	**Definition**	**Treated IR per 100 PY (95% CI)**	**Notes & Uncertainties**
		Risks (Unfavorable Effects)	

Effects Table of Key Benefits and Risks - RWE Study 747-405			
Treatment-Emergent Adverse Events of Special Interest	Coded medical encounter observed during treatment follow-up if (a) not observed during the entire pre-index period or (b) observed during the pre-index period but then observed in a worsened state during treatment follow-up	Incidence Rates per 100 PY: Hepatic: 49.5 OCA vs. 54.4 control Dyslipidemia: 14.8 OCA vs. 16.3 control Cholecystitis/Cholelithiasis: 10.9 OCA vs. 13.0 control Renal: 8.9 OCA vs. 13.4 Control Pruritus: 7.9 OCA vs. 6.4 Control Cardiovascular: 7.0 OCA vs. 7.5 control	- Study 747-405 was not designed to evaluate these outcomes

FOOTNOTE: (1) As-Treated analyses conducted by the Applicant are similar to a "While On-Treatment" analysis strategy and include several censoring criteria that define Treatment Switch. (2) ITT2 analyses conducted by the Applicant relax some of the censoring rules in the As-Treated analysis (3) FDA ITT analysis of time to death or liver transplant is closest to a true ITT analysis because it doesn't consider any censoring rules other than end of study on 31 Dec 2021.

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Guidance for industry

Guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products* (July 2024)

ICH Harmonised Guideline *Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1)* (November 2019)

8 Appendix

8.1 Study 747-301 Additional Information

The patient disposition and baseline clinical characteristics in Trial 747-301 are presented in Table 20 and Table 21, respectively. A greater percentage of subjects in the OCA arm discontinued the trial due to pruritus compared to the placebo arm. Baseline characteristics were generally balanced across the treatment arms.

Table 20. Patient Disposition, ITT Population, Study 747-301

Parameter	OCA 10 mg N=73 n (%)	OCA Titration N=71 n(%)	Placebo N=73 n (%)
Patients randomized	73 (100%)	71 (100%)	73 (100%)
mITT and safety populations	73 (100%)	70 (98.6%)	73 (100%)
Discontinued study	9 (12.3%)	7 (9.9%)	3 (4.1%)
Pruritus	7 (9.6%)	1 (1.4%)	0
Other adverse events	1 (1.4%)	3 (4.2%)	2 (2.7%)
Death	0	1 (1.4%)	0
Withdrawal by subject	1 (1.4%)	2 (2.8%)	1 (1.4%)

Source: Statistical Review of Study 737-301, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000TOC.cfm.

Abbreviations: OCA, obeticholic acid; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group

Table 21. Baseline Clinical Characteristics, mITT Population, Trial 747-301

Characteristic	OCA 10 mg N=73 n (%)	OCA Titration N=70 n (%)	Placebo N=73 n (%)
Baseline UDCA use, n (%)			
Yes	67 (91.8%)	65 (92.9%)	68 (93.2%)
No	6 (8.2%)	5 (7.1%)	5 (6.9%)
ALP, U/L			
Mean (SD)	316.3 (103.9)	325.9 (116.2)	327.5 (115.0)
Median (min, max)	271.3 (207, 620)	281.3 (187, 811)	311.9 (144, 746)
TB, mg/dL			
Mean (SD)	0.7 (0.4)	0.6 (0.3)	0.7 (0.4)
Median (min, max)	0.5 (0.1, 2.0)	0.5 (0.1, 2.1)	0.5 (0.1, 2.3)
Baseline Rotterdam criteria, n (%)			
Early	65 (89.0%)	64 (91.4%)	66 (90.4%)
Moderate	8 (11.0%)	6 (8.6%)	7 (9.6%)
Advanced	0	0	0

Source: Statistical Review of Study 747-301, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000TOC.cfm.

Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation; ALP, alkaline phosphatase; TB, total bilirubin

8.2 Subject Characteristics Across OCA PBC Trials

Table 22 displays the baseline clinical characteristics across Trials 747-301, 747-302, and 747-401. There are limitations to cross-trial comparisons. However, based on the Child-Pugh Class and Rotterdam criteria, Trial 747-301 enrolled subjects with the least-severe disease, followed by the Trial 747-302

USPI-labeled population, the Trial 747-302 USPI-contraindicated population, and Trial 747-401. Mean baseline TB was 0.7 mg/dL for Trial 747-301, 1.2 mg/dL for the Trial 747-302 USPI-labeled population, 2.0 mg/dL for the Trial 747-302 USPI-contraindicated population, and 3.1 mg/dL for Trial 747-401. However, ALP, ALT, and AST did not show clear trends associated with disease severity, i.e., ALP does not necessarily increase as disease became more severe.

Table 22. Baseline Disease Characteristics Across Trials

	Trial 747-301	Trial 747-302			Trial 747-401
Characteristic	ITT Population N=216	USPI-Labeled N=149	USPI-Contraindicated N=185	ITT Population N=334	ITT Population N=22
Cirrhosis group[1], n (%)					
Cirrhotic	0	9 (6.0)	185 (100.0)	194 (58.1)	0
Noncirrhotic	0	140 (94.0)	0	140 (41.9)	0
Missing	216 (100.0)	0	0	0	22 (100.0)
Child-Pugh class, n (%)					
A	0	146 (98.0)	127 (68.6)	273 (81.7)	0
B	0	0	55 (29.7)	55 (16.5)	21 (95.5)
C	0	0	0	0	1 (4.5)
Not evaluable	0	1 (<1)	0	1 (<1)	0
Missing	216 (100.0)	2 (1.3)	3 (1.6)	5 (1.5)	0
Rotterdam Criteria, n (%)					
Early	174 (80.6)	85 (57.0)	21 (11.4)	106 (31.7)	5 (22.7)
Moderate	36 (16.7)	63 (42.3)	143 (77.3)	206 (61.7)	10 (45.5)
Advanced	6 (2.8)	1 (<1)	21 (11.4)	22 (6.6)	7 (31.8)
Alkaline phosphate (ALP) (U/L)					
N	216	149	185	334	22
Mean (SD)	323 (111)	582 (284)	416 (265)	490 (285)	252 (121)
Median	287	558	344	434	233
IQR	238, 373	390, 734	206, 558	262, 652	151, 367
Min, max	144, 811	54, 1495	68, 1526	54, 1526	91, 491
Total bilirubin (mg/dL)					
N	216	149	185	334	22
Mean (SD)	0.7 (0.4)	1.2 (0.6)	2.0 (0.7)	1.6 (0.8)	3.1 (2.1)
Median	0.5	1.1	1.8	1.5	2.7
IQR	0.4, 0.8	0.7, 1.6	1.5, 2.4	1.0, 2.0	1.4, 4.7
Min, max	0.1, 2.3	0.2, 2.8	0.4, 4.0	0.2, 4.0	0.6, 7.4
AST (U/L)					
N	216	149	185	334	22
Mean (SD)	50 (26)	80 (39)	83 (38)	82 (39)	75 (36)
Median	44	73	77	75	60
IQR	32, 60	51, 101	55, 101	54, 101	46, 103
Min, max	20, 186	18, 224	14, 195	14, 224	28, 151
ALT (U/L)					
N	216	149	185	334	22
Mean (SD)	58 (36)	92 (50)	75 (51)	83 (51)	49 (24)
Median	49	84	60	73	44
IQR	35, 69	55, 116	37, 101	43, 105	31, 59
Min, max	16, 245	20, 267	14, 315	14, 315	18, 101

Source: Statistical analyst analysis using Applicant submitted datasets adsl.xpt, adlb.xpt and adresp.xpt.

[1] Key exclusion criteria for Trial 747-301 included presence of cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin>2xULN. Key inclusion criteria for Trial 747-401 included evidence of cirrhosis.

Abbreviations: IQR, interquartile range, ITT, Intention-to-treat population, N, number of subjects, SD, standard deviation

8.3 Trial 747-302 Additional Information

8.3.1 Key Trial Dates

- December 26, 2014: first subject informed consent
- September 2020: The DMC reviewed the first interim-analysis results. Based on the closed DMC minutes (i.e., not available to personnel besides the DMC), "the DMC felt the study would likely have been futile if a reasonable futility bound had been available." The closed DMC minutes further stated, "Since the study did not have a futility bound, the DMC agreed they would not terminate the study for futility at that time."
- December 2020: DMC recommended to the Applicant no further enrollment of patients into the postmarketing studies. The DMC stated, "Study 747-302 (COBALT) is unlikely to provide evidence of efficacy for the enrolled PBC population as an aggregate or in any subpopulation", and "Given the high likelihood of futility of both Studies" (i.e., Study 747-302, and Study 747-401), "the DMC recommends no further enrollment of these postmarketing studies."
- Enrollment was stopped (last subject randomized on December 2, 2020); however, the study was not terminated at that time. The Agency encouraged the Applicant to continue dosing of patients already enrolled in Trial 747-302, because these data would provide optimal information for safety and efficacy of OCA use in the PBC population.
- May 2021: The USPI was revised, which contraindicated the use of OCA in patients with decompensated cirrhosis or a prior decompensation event and those with compensated cirrhosis with evidence of portal hypertension. The labeling change required that 55% (185/334) of the subjects in Trial 747-302 be discontinued from the investigational product. These contraindicated subjects stayed in the study for follow-up.
- September 2021 to March 2022: To improve power, the primary endpoint was expanded prior to unblinding. Discussion between the Applicant and the Agency regarding the change in the primary endpoint started in September 2021, and the Statistical Analysis Plan was finalized in March 2022.
- At the time of study termination, the study had accrued 151 expanded primary endpoint events; the target was 127 events in the ITT population.
- December 23, 2021: Final visit of the last subject

8.3.2 Baseline Characteristics

Table 23 displays the baseline demographics and clinical characteristics of the USPI-labeled, USPI-contraindicated, and ITT populations in Trial 747-302. These characteristics were generally balanced across the treatment groups within each analysis population. Baseline disease severity varied across analysis populations, as expected.

Table 23. Baseline Demographics and Clinical Characteristics, Trial 747-302

	USPI-Labeled		USPI-Contraindicated		ITT Population	
	OCA N=81	Placebo N=68	OCA N=87	Placebo N=98	OCA N=168	Placebo N=166
Characteristic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex, n (%)						
Male	10 (12.3%)	5 (7.4%)	7 (8.0%)	12 (12.2%)	17 (10.1%)	17 (10.2%)
Female	71 (87.7%)	63 (92.6%)	80 (92.0%)	86 (87.8%)	151 (89.9%)	149 (89.8%)
Age, years						
Mean (SD)	51.1 (9.8)	52.6 (10.9)	55.6 (10.3)	54.8 (10.0)	53.4 (10.3)	53.9 (10.4)
Median (min, max)	52 (29, 70)	52 (32, 77)	56 (29, 75)	56 (30, 77)	53.5 (29, 75)	54 (30, 77)
Age group (years), n (%)						
≥17 to <65	71 (87.7%)	57 (83.8%)	69 (79.3%)	83 (84.7%)	140 (83.3%)	140 (84.3%)
≥65 to <75	10 (12.3%)	9 (13.2%)	17 (19.5%)	13 (13.3%)	27 (16.1%)	22 (13.3%)
≥75	-	2 (2.9%)	1 (1.1%)	2 (2.0%)	1 (0.6%)	4 (2.4%)
Race, n (%)						
American Indian or Alaska Native	1 (1.2%)	1 (1.5%)	-	1 (1.0%)	1 (0.6%)	2 (1.2%)
Asian	4 (4.9%)	6 (8.8%)	7 (8.0%)	3 (3.1%)	11 (6.5%)	9 (5.4%)
Black or African American	1 (1.2%)	-	1 (1.1%)	2 (2.0%)	2 (1.2%)	2 (1.2%)
White	70 (86.4%)	58 (85.3%)	76 (87.4%)	85 (86.7%)	146 (86.9%)	143 (86.1%)
Other	2 (2.5%)	-	2 (2.3%)	1 (1.0%)	4 (2.4%)	1 (0.6%)
Not Reported	3 (3.7%)	3 (4.4%)	1 (1.1%)	6 (6.1%)	4 (2.4%)	9 (5.4%)
Ethnicity, n (%)						
Hispanic	13 (16.0%)	6 (8.8%)	11 (12.6%)	12 (12.2%)	24 (14.3%)	18 (10.8%)
Non-Hispanic	63 (77.8%)	59 (86.8%)	75 (86.2%)	80 (81.6%)	138 (82.1%)	139 (83.7%)
Unknown	5 (6.2%)	3 (4.4%)	1 (1.1%)	6 (6.1%)	6 (3.6%)	9 (5.4%)
Country of participation, n (%)						
United States	10 (12.3%)	10 (14.7%)	20 (23.0%)	21 (21.4%)	30 (17.9%)	31 (18.7%)
Canada	5 (6.2%)	3 (4.4%)	11 (12.6%)	12 (12.2%)	16 (9.5%)	15 (9.0%)
United Kingdom	4 (4.9%)	7 (10.3%)	8 (9.2%)	7 (7.1%)	12 (7.1%)	14 (8.4%)
Italy	8 (9.9%)	5 (7.4%)	6 (6.9%)	5 (5.1%)	14 (8.3%)	10 (6.0%)
Argentina	17 (21.0%)	8 (11.8%)	7 (8.0%)	6 (6.1%)	24 (14.3%)	14 (8.4%)
Poland	2 (2.5%)	2 (2.9%)	5 (5.7%)	10 (10.2%)	7 (4.2%)	12 (7.2%)
Other[1]	35 (43.2%)	33 (48.5%)	30 (34.5%)	37 (37.8%)	65 (38.7%)	70 (42.2%)

Characteristic	USPI-Labeled OCA N=81 n (%)	USPI-Labeled Placebo N=68 n (%)	USPI-Contraindicated OCA N=87 n (%)	USPI-Contraindicated Placebo N=98 n (%)	ITT Population OCA N=168 n (%)	ITT Population Placebo N=166 n (%)
Baseline bilirubin, n (%)						
>ULN[2]	39 (48.1%)	28 (41.2%)	79 (90.8%)	89 (90.8%)	118 (70.2%)	117 (70.5%)
≤ULN	42 (51.9%)	40 (58.8%)	8 (9.2%)	9 (9.2%)	50 (29.8%)	49 (29.5%)
Baseline total bilirubin, mg/dL						
Mean (SD)	1.2 (0.6)	1.2 (0.6)	1.9 (0.7)	2.0 (0.8)	1.6 (0.8)	1.7 (0.8)
Baseline ALP, U/L						
Mean (SD)	549.7 (270.7)	620.2 (296.6)	417.5 (268.3)	415.5 (263.6)	481.3 (276.7)	499.3 (294.5)
Baseline platelets, 10^9/L						
Mean (SD)	270.0 (77.0)	258.0 (95.2)	154.1 (89.8)	155.8 (85.7)	209.9 (101.8)	197.2 (102.6)
Baseline UDCA use, n (%)						
Yes	68 (84.0%)	58 (85.3%)	79 (90.8%)	89 (90.8%)	147 (87.5%)	147 (88.6%)
No	13 (16.0%)	10 (14.7%)	8 (9.2%)	9 (9.2%)	21 (12.5%)	19 (11.4%)
Baseline disease stage per USPI, n (%)						
Labeled	81 (100%)	68 (100%)	-	-	81 (48.2%)	68 (41.0%)
Contraindicated	-	-	87 (100%)	98 (100%)	87 (51.8%)	98 (59.0%)
Baseline disease stage, n (%)						
Noncirrhotic	78 (96.3%)	62 (91.2%)	-	-	78 (46.4%)	62 (37.3%)
Compensated cirrhosis	3 (3.7%)	6 (8.8%)	55 (63.2%)	61 (62.2%)	58 (34.5%)	67 (40.4%)
Decompensated cirrhosis	-	-	32 (36.8%)	37 (37.8%)	32 (19.0%)	37 (22.3%)
Baseline Rotterdam criteria, n (%)						
Early	45 (55.6%)	40 (58.8%)	10 (11.5%)	11 (11.2%)	55 (32.7%)	51 (30.7%)
Moderate	35 (43.2%)	28 (41.2%)	67 (77.0%)	76 (77.6%)	102 (60.7%)	104 (62.7%)
Advanced	1 (1.2%)	-	10 (11.5%)	11 (11.2%)	11 (6.5%)	11 (6.6%)
Baseline Child-Pugh Class, n (%)						
A	80 (98.8%)	66 (97.1%)	63 (72.4%)	64 (65.3%)	143 (85.1%)	130 (78.3%)
B	-	-	24 (27.6%)	31 (31.6%)	24 (14.3%)	31 (18.7%)
Not evaluable or missing	1 (1.2%)	2 (2.9%)	-	3 (3.1%)	1 (0.6%)	5 (3.0%)
Baseline Child-Pugh score						
Mean (SD)	5.2 (0.4)	5.2 (0.4)	5.9 (0.9)	5.9 (1.0)	5.5 (0.8)	5.6 (0.9)
Baseline MELD score						
Mean (SD)	7.5 (1.2)	7.5 (1.2)	9.4 (1.6)	9.6 (1.7)	8.5 (1.7)	8.7 (1.8)

Source: Clinical Study Report 747-302 (pp. 264-277); findings reproduced by the statistical reviewer using adsl.xpt.

[1] Other countries include Australia, Austria, Belgium, Brazil, Switzerland, Chile, Germany, Denmark, Spain, Estonia, Finland, France, Hong Kong, Hungary, Israel, South Korea, Lithuania, Mexico, Netherlands, Sweden, Turkey

[2] Total bilirubin ULN=1.2 mg/dL (Female and Male)

Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SD, standard deviation; UDCA, ursodeoxycholic acid; USPI, United States Prescribing Information; ULN, upper limit of normal; ALP, alkaline phosphatase

8.3.3 Subject Disposition

The disposition of subjects in the USPI-labeled population is summarized in Table 24. Approximately 64% of USPI-labeled subjects remained in the trial until its closure by the Applicant. A total of 44% of OCA-randomized subjects and 29% of placebo-randomized subjects were still taking study drug when the trial was closed. The most common reason for treatment discontinuation was an adverse event (OCA 34.6% versus placebo 32.4%).

Table 24. Patient Disposition, USPI-Labeled Population, Trial 747-302[1]

Parameter	OCA N=81 n (%)	Placebo N=68 n (%)	Total Population N=149 n (%)
On study at time of study closure	54 (66.7%)	42 (61.8%)	96 (64.4%)
Discontinued trial			
Adverse event	4 (4.9%)	7 (10.3%)	11 (7.4%)
Death	4 (4.9%)	1 (1.5%)	5 (3.4%)
Lost to follow-up	3 (3.7%)	3 (4.4%)	6 (4.0%)
Withdrawal by subject	9 (11.1%)	6 (8.8%)	15 (10.1%)
Physician decision	-	4 (5.9%)	4 (2.7%)
Site closure	2 (2.5%)	2 (2.9%)	4 (2.7%)
COVID-19 limitation	2 (2.5%)	-	2 (1.3%)
Other	3[a] (3.7%)	3[b] (4.4%)	6 (4.0%)
On study drug at time of study closure	36 (44.4%)	20 (29.4%)	56 (37.6%)
Discontinued study drug			
Adverse event	28 (34.6%)	22 (32.4%)	50 (33.6%)
Initiated commercial OCA	4 (4.9%)	8 (11.8%)	12 (8.1%)
Physician decision	1 (1.2%)	6 (8.8%)	7 (4.7%)
Noncompliance with study drug	-	2 (2.9%)	2 (1.3%)
Protocol violation	-	1 (1.5%)	1 (0.6%)
Site closure	3 (3.7%)	1 (1.5%)	4 (2.7%)
COVID-19 limitation	1 (1.2%)	-	1 (0.6%)
Withdrawal by subject	5 (6.2%)	6 (8.8%)	11 (7.4%)
Lost to follow-up	1 (1.2%)	1 (1.5%)	2 (1.3%)
Other	2[c] (2.5%)	1[d] (1.5%)	3 (2.0%)

Source: Clinical Study Report Addendum 747-302 (pp. 34-35); findings reproduced by the statistical reviewer using adsl.xpt
[1] Duration was up to study termination by the Sponsor.
[a] One subject: liver transplant, one subject: liver transplant waitlist, one subject: patient started another intervention study.
[b] One subject: liver transplant waitlist, one subject: study close-out, one subject: missing.
[c] One subject: Per Sponsor request due to label change, one subject: liver transplant.
[d] One subject: Per Sponsor request due to label change.
Abbreviations: COVID-19, coronavirus disease 2019; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified population or group; OCA, obeticholic acid; USPI, United States Prescribing Information

8.3.4 Extent of Exposure

The mean (SD) durations of exposure to obeticholic acid in 747-302 were OCA (168 subjects) 29.5 months and placebo (166 subjects) 25.1 months (Table 25).

Table 25. Duration of Exposure USPI-Labeled and USPI Contraindicated, Study 747-302

	USPI-Labeled		USPI-Contraindicated	
Parameter	**OCA N=81**	**Placebo N=68**	**OCA N=87**	**Placebo N=98**
Duration of treatment, months				
Mean (SD)	31.4 (20.7)	25.2 (17.7)	27.8 (21.8)	25 (17.1)
Median (Q1, Q3)	29.6 (14.1, 49.6)	19 (11.8, 40.8)	21.1 (8.7, 48.1)	20.9 (12.1, 33.9)
Min, max	0.3, 71.7	1.1, 72.1	0.1, 71.7	1.3, 67.8
Total exposure (person-years)	212	143	202	204
Patients treated, by duration, n (%)				
<2 months	6 (7.4)	2 (2.9)	5 (5.7)	2 (2.0)
≥2 to <4 months	4 (4.9)	3 (4.4)	5 (5.7)	3 (3.1)
≥4 to <8 months	6 (7.4)	5 (7.4)	9 (10.3)	8 (8.2)
≥8 to <16 months	8 (9.9)	18 (26.5)	19 (21.8)	24 (24.5)
≥16 to <24 months	10 (12.3)	10 (14.7)	7 (8.0)	20 (20.4)
≥24 to <32 months	13 (16.0)	7 (10.3)	10 (11.5)	14 (14.3)
≥32 to <40 months	4 (4.9)	5 (7.4)	5 (5.7)	8 (8.2)
≥40 to <48 months	9 (11.1)	11 (16.2)	4 (4.6)	6 (6.1)
≥48 to <56 months	5 (6.2)	3 (4.4)	9 (10.3)	6 (6.1)
≥56 to <64 months	13 (16.0)	3 (4.4)	10 (11.5)	4 (4.1)
≥64 to <72 months	3 (3.7)	0	4 (4.6)	3 (3.1)
≥72 to <80 months	0	1 (1.5)	0	0
≥ 80 months	0	0	0	0

Source: adex.xpt and adsl.xpt; software: R.

Duration is up to 2196 days.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OCA, obeticholic acid; Q1, first quartile; Q3, third quartile; SD, standard deviation; USPI, United States Prescribing Information

Subjects' time on-treatment (i.e., until treatment discontinuation) and time on-study (i.e., until the last contact) for the USPI-labeled population are presented in Table 26.

Table 26. Time on Study and Time on Treatment, USPI-Labeled Population, Trial 747-302

Characteristic	**OCA N=81**	**Placebo N=68**
Time on-treatment[1] (months)		
Mean (SD)	31.3 (20.7)	25.2 (17.7)
Median (Q1, Q3)	29.6 (13.6, 51.0)	19.0 (11.7, 40.9)
Time on-study[2] (months)		
Mean (SD)	41.7 (18.6)	40.3 (19.1)
Median (Q1, Q3)	42.1 (28.3, 59.7)	42.7 (24.0, 58.6)

Source: Statistical reviewer analysis using Applicant submitted dataset adsl.xpt.

[1] Difference between treatment start date and treatment end date.

[2] Difference between randomization date and last contact date.

Abbreviations: OCA, obeticholic acid; N, number of patients in treatment arm; SD, standard deviation

8.3.5 Use of Commercial OCA and Concomitant Medication

Use of commercial OCA and concomitant medications in the USPI-labeled population in Trial 747-302 is presented in Table 27. There was more commercial OCA use in the placebo arm (12%) compared to the

OCA arm (5%) in the USPI-labeled population; however, the use of other concomitant medications was similar across the two arms.

Table 27. Use of Commercial OCA and Concomitant Medication, USPI-Labeled Population, Trial 747-302

	OCA N=81			Placebo N=68		
Medication	**Newly Started**	**Dose Increased**	**Total**	**Newly Started**	**Dose Increased**	**Total**
Commercial OCA, n (%)	4 (5%)	-	4 (5%)	8 (12%)	-	8 (12%)
Concomitant medication, n (%)	13 (16%)	7 (9%)	20 (25%)	18 (26%)	4 (6%)	22 (32%)
UDCA	2 (2%)	6 (7%)	8 (10%)	6 (9%)	3 (4%)	9 (13%)
Fibrate	12 (15%)	1 (1%)	13 (16%)	12 (18%)	0 (0%)	12 (18%)
Oral budesonide	1 (1%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)	2 (3%)

Source: Statistical reviewer's analysis using the Applicant-submitted dataset adsl2.xpt.
Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic

8.3.6 Additional Efficacy Assessments

Kaplan-Meier estimates of the probabilities of experiencing an event as defined for the primary endpoint and key secondary endpoints by Years 1, 2, 3, and 4 are presented in Table 28.

Table 28. Kaplan Meier Estimates of Probability of Experiencing an Event, Trial 747-302

	ITT Population		USPI-Labeled	
Endpoints	**OCA**	**Placebo**	**OCA**	**Placebo**
Time Points	**N=168**	**N=166**	**N=81**	**N=68**
Expanded primary endpoint				
Year 1	24.5%	18.4%	14.1%	10.6%
Risk difference (95% CI)[1]	6.2% (-2.7, 15.1)		3.5% (-7.2, 14.2)	
Year 2	33.8%	37.9%	19.5%	20.5%
Risk difference (95% CI)	-4.1% (-14.7, 6.6)		-1.1% (-14.4, 12.3)	
Year 3	40.0%	49.5%	25.6%	27.0%
Risk difference (95% CI)	-9.5% (-21.0, 1.9)		-1.3% (-16.7, 14.0)	
Year 4	45.1%	55.7%	27.6%	31.7%
Risk difference (95% CI)	-10.6% (-22.6, 1.5)		-4.0% (-20.4, 12.3)	
Key secondary endpoint: Primary endpoint prior to expansion				
Year 1	13.1%	6.2%	3.9%	1.6%
Risk difference (95% CI)	6.9% (0.5, 13.3)		2.4% (-2.9, 7.7)	
Year 2	18.5%	18.3%	6.7%	6.6%
Risk difference (95% CI)	0.2% (-8.4, 8.9)		0.1% (-8.3, 8.5)	
Year 3	25.0%	29.3%	15.1%	11.0%
Risk difference (95% CI)	-4.2% (-14.7, 6.3)		4.1% (-8.1, 16.2)	
Year 4	32.4%	33.6%	17.5%	11.0%
Risk difference (95% CI)	-1.2% (-12.9, 10.6)		6.4% (-6.4, 19.3)	
Key secondary endpoint: Group 1 event				
Year 1	13.1%	6.8%	3.9%	3.1%
Risk difference (95% CI)	6.3% (-0.2, 12.8)		0.8% (-5.2, 6.9)	
Year 2	19.2%	19.6%	6.7%	8.1%
Risk difference (95% CI)	-0.4% (-9.3, 8.5)		-1.5% (-10.3, 7.4)	
Year 3	25.7%	29.8%	15.1%	12.5%
Risk difference (95% CI)	-4.1% (-14.6, 6.5)		2.6% (-9.8, 15.0)	
Year 4	33.0%	34.0%	17.5%	12.5%
Risk difference (95% CI)	-1.0% (-12.8, 10.7)		5.0% (-8.1, 18.0)	
Key secondary endpoint: Liver transplant or death				
Year 1	5.7%	1.8%	2.6%	0%
Risk difference (95% CI)	3.9% (-0.3, 8.1)		2.6% (-1.0, 6.2)	
Year 2	12.0%	7.6%	5.4%	1.8%
Risk difference (95% CI)	4.4% (-2.4, 11.1)		3.7% (-2.5, 9.9)	
Year 3	17.0%	15.8%	12.0%	4.2%
Risk difference (95% CI)	1.2% (-7.8, 10.2)		7.8% (-1.9, 17.6)	
Year 4	24.8%	21.5%	16.8%	4.2%
Risk difference (95% CI)	3.3% (-7.8, 14.4)		12.7% (1.3, 24.1)	

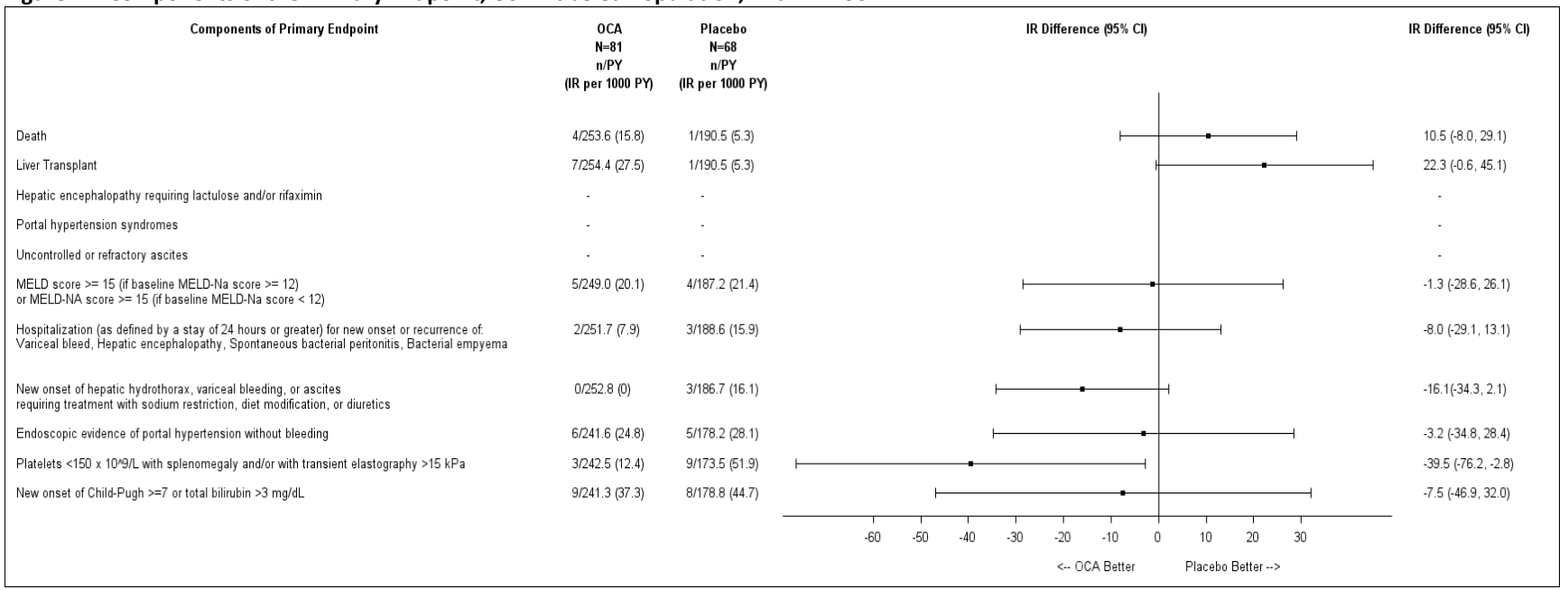
Source: Statistical reviewer's analysis using the Applicant-submitted datasets adtte.xpt and adsl.xpt.

[1] Difference is shown between OCA versus placebo.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; OCA, obeticholic acid; N, number of subjects in treatment arm

Figure 11 shows the incidence rate of each component of the primary endpoint for the USPI-labeled population.

Figure 11. Components of the Primary Endpoint, USPI-Labeled Population, Trial 747-302



Source: Statistical reviewer analysis using Applicant submitted dataset adevt,xpt

[1]According to the Applicant, if an expanded endpoint components trigger occurred after any positively adjudicated endpoint event, the trigger was not sent for adjudication. Thus, the expanded endpoint components may not be reliably captured in this analysis.

[2]The incidence rate (IR) is calculated by dividing the number of subjects who experienced the event by the total number of patient-years (PYs) of at-risk time and multiplying by 1000. At-risk time for a subject who experienced an event is time from randomization to the first event, and at-risk time for a subject who did not experience an event is time from randomization to end of study. Analysis of each component ignores the occurrence of other components and important intercurrent events (e.g., deaths)

[3] IR difference is calculated by subtracting the IR of events in the placebo arm from the IR of events in the OCA arm

The 95% confidence interval was calculated based on normal approximation and $\hat{\sigma}(IR) = \sqrt{n/PY^2}$

Abbreviations: CI, confidence interval; IR, incidence rate; N, number of subjects in treatment arm; n, number of subjects with event; OCA, obeticholic acid; PY, patient-years

Table 29 summarizes the number of liver transplants and deaths that occurred in the trial. In the USPI-labeled population, one death was observed in the placebo arm compared to four deaths in the OCA arm. One liver transplant was observed in the placebo arm compared to seven in the OCA arm. See the results of the key secondary endpoint of time to liver transplant or all-cause death in Figure 4.

Table 29. Numbers of Liver Transplants and All-Cause Deaths, Trial 747-302

	USPI-Labeled		USPI-Contraindicated		ITT Population	
Endpoint	OCA N=81	Placebo N=68	OCA N=87	Placebo N=98	OCA N=168	Placebo N=166
Death or liver transplant, n (%)	11	2	23	27	34	29
Death, n (%)	4	1	12	11	16	12
Liver transplant, n (%)	7	1[a]	13[b]	17[c]	20[b]	18[c]

Source: Statistical reviewer using Applicant submitted dataset adtte.xpt.

[a] Occurred after the initiation of commercial OCA.

[b] Two subjects died after liver transplant.

[c] One subject died after liver transplant.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with given characteristic; OCA, obeticholic acid

8.3.6.1 Subgroup Analyses

The results of subgroup analyses by demographic subgroups and disease characteristics based on the primary endpoint and comparing subjects randomized to OCA versus placebo were consistent with the findings in the overall population, with some variability from the smaller subgroups.

8.3.7 Subject-Level Assessments

Table 30 shows the USPI-labeled subjects who received liver transplant in Trial 747-302.

Overall Assessment

Six of the eight subjects were noncirrhotic at baseline. The mean and median times to OCA discontinuation were 544.1 days (1.5 years) and 602 days (1.6 years) with ranges of 199 days to 912 days, respectively. The mean and median times to liver transplantation were 1116.8 days (3 years) and 602 days (3.2 years) with ranges of 639 days to 1412 days after OCA was initiated. The average age of subjects who underwent liver transplantation was 46 years (range 40 to 58 years).

Most subjects required liver transplantation for worsening of liver function, except two subjects in whom pruritus was noted as the reason for liver transplantation.

Table 30. Clinical Indication, Time on Study for Subjects Requiring Liver Transplantation, USPI-labeled Population, Trial 747-302

Subject/ Age/Sex	Cirrhosis Status	Treatment Arm	Last Day IP /OLT Study Day	Review Findings
1 47/F	Noncirrhotic	Placebo USPI-labeled for <1 year, then received commercial OCA for 2 years	268/1078 Commercial OCA: 269-985/1078	Subject initially randomized to placebo and switched to commercial OCA on Day 268. Subject received OCA for a little over 2 years. While subject was on OCA, experienced multiple portal hypertensive bleeding, and ascites.

Subject/ Age/Sex	Cirrhosis Status	Treatment Arm	Last Day IP /OLT Study Day	Review Findings
2/ 49/M	Noncirrhotic	OCA USPI-labeled	912/1580	While on OCA, subject had progressive increase in bilirubin, episodes of recurrent anemia, portal hypertensive bleeding.
3/ 40/F	Noncirrhotic	OCA USPI-labeled	611/1412	Subject with increase in bilirubin, from a baseline value 1.8 mg/dL to 4.1 mg/dL, developed cirrhosis and progressed from CP score of 5 to 8 (i.e., CP A to CP B) while on OCA
4/ 43/F	Cirrhotic	OCA USPI-labeled	667/812	Subject with increasing bilirubin and MELD score while she was on OCA and progressed despite discontinuation of OCA
5/ 44/F	Noncirrhotic	OCA USPI-labeled	593/1356	Subject with worsened pruritus on OCA, biopsy showed noncirrhotic PBC. Progressive jaundice leading to liver transplant.
6/ 58/F	Noncirrhotic	OCA USPI-labeled	221/234	Subject with pruritus as indication for liver transplant; bilirubin 0.6 mg/dL, MELD 6.4. Explant showed stage 2 fibrosis and ductopenia.
7/ 43/F	Cirrhotic	OCA USPI-labeled	199/639	Subject with increased bilirubin and transaminases and CP score on OCA (5 to 7), progression to liver transplant
8/ 43/F	Noncirrhotic	OCA USPI-labeled	434/823	Subject with progressive jaundice, recurrent pruritus prior to liver transplant

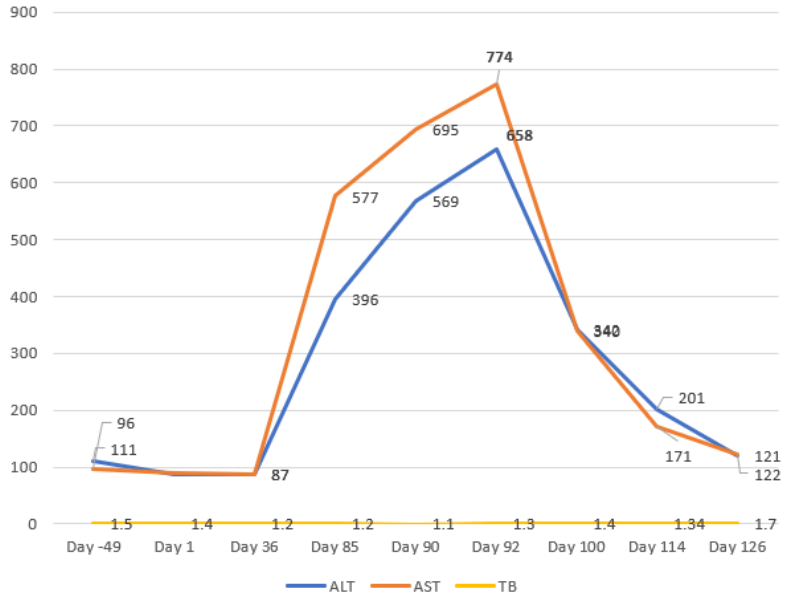
Source: Clinical reviewer generated table from Clinical Study Report and HOC narratives submitted by the Applicant.
Abbreviations: P: Child Pugh; EV: esophageal varices; MELD model for end-stage liver disease; GIB: gastrointestinal bleed; HE: hepatic encephalopathy; ESLD: end-stage liver disease; OLT: orthotopic liver transplant; PNF: primary nonfunction; ACLF, acute on liver failure; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; dBil., direct bilirubin; DILI, drug-induced liver injury; TB, total bilirubin; IP, investigational product (OCA)

8.3.7.1.1.1 Subject 15

A 57-year-old female with PBC stage 1 diagnosed by liver biopsies in 1998 and 2000, with a past medical history of autoimmune thyroiditis, arthralgias, xanthelasma, and pruritus. Concomitant medications included UDCA (1000 mg/day), cholestyramine, and L-thyroxine. She started OCA 5 mg, daily. On Day 14, she experienced worsening of pruritus and was started on rifampicin 150 mg. Markedly elevated transaminases were noted on Day 85 and these worsened by Day 90. Rifampicin was discontinued. A liver biopsy was obtained, consistent with PBC fibrosis stage 2 to 3, with “slight plasma cell proliferation” suggestive of possible overlap with autoimmune hepatitis. The hepatic venous pressure gradient wedge was 5 mm Hg (i.e., no evidence of portal hypertension). After discontinuing OCA, ALT and AST improved without use of corticosteroids or other therapy, indicative of a positive dechallenge.

The differential diagnosis for this case of marked elevations of ALT and AST while on OCA includes DILI due to OCA, DILI due to rifampicin, AIH overlap, and PBC flare.

Figure 12. DILI Case Review #1: Liver Tests Over the Trial Timeline



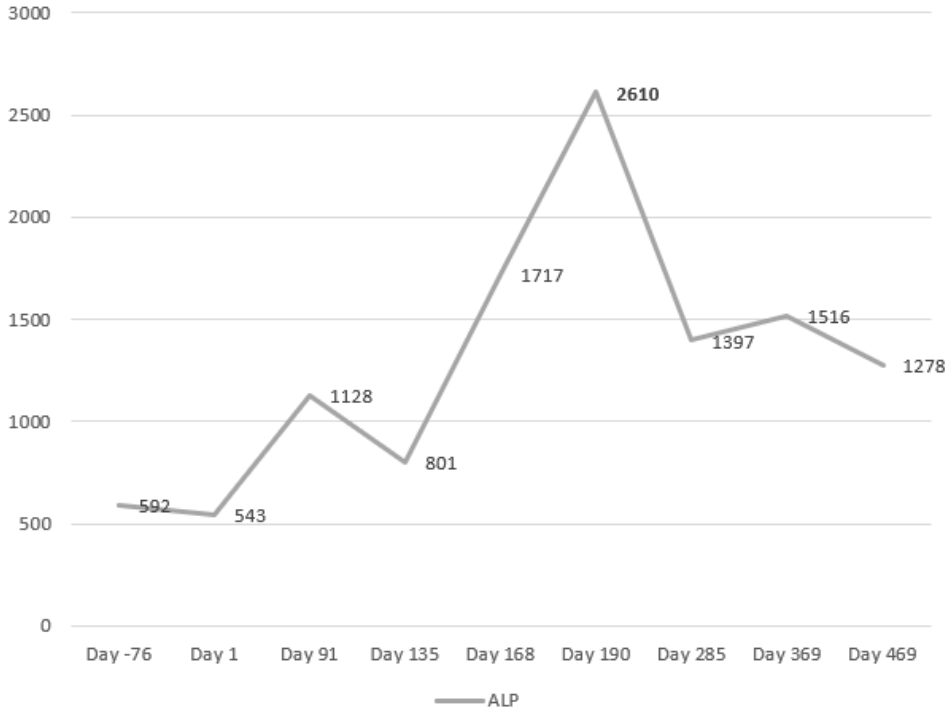
Study Day	Day -49	Start IP Day 1	Day 36	Day 85	Day 90	Day 92	Day 100	Day 114	Day 126
ALT	111	87	87	396	569	658	342	201	121
AST	96	90	87	577	695	774	340	171	122
ALP	733	585	505	567	548	452	361	NA	327
TB	1.5	1.4	1.2	1.2	1.1	1.3	1.4	1.34	1.7

Source: Generated by the Clinical Reviewer using data submitted by the Applicant in the AdaM datasets.

Subject 16

A 69-year-old female diagnosed with PBC in 2001. The diagnosis was confirmed by liver biopsy, which showed PBC with stage 1 fibrosis. Her past medical history included duodenal ulcer requiring subtotal gastrectomy, hypertension, cerebral ischemia, carotid arteriosclerosis, and acalculous sialadenitis. Medications prior to enrollment in the trial included enalapril, acetylsalicylic acid, and iron. Subject started OCA 5 mg and on Day 91 her ALP was markedly elevated, 1128 U/L. Her baseline ALP was 543 U/L. OCA was up titrated up to 10 mg daily on Day 111 and she then experienced pruritis that required a dose reduction to 10 mg every other day. ALP continued to increase and peaked at 2610 U/L, leading to discontinuation of OCA on Day 241 for pruritis and rash. ALP began to decrease and improved after OCA was discontinued.

Figure 13. DILI Case Review: ALP Over the Trial Timeline



Study Day	Day -76	Day 1	Day 91	Day 135	Day 168	Day 190	Day 285	Day 369	Day 469
ALT	25	17	27	19	51	36	42	50	13
AST	31	22	23	20	84	34	46	75	26
ALP	592	543	1128	801	1717	2610	1397	1516	1278
TBILI	0.3	0.3	0.48	0.37	0.73	0.58	0.63	0.36	0.35

Source: Generated by the Clinical Reviewer using data submitted the Applicant in AdaM datasets.

Surrogate Endpoint (ALP) Results

At Month 12, 10% of OCA-randomized subjects and 2% of placebo-randomized subjects achieved the biochemical response (Table 31).

Table 31. Biochemical Response at Month 12, ITT Population, Trial 747-302

Variable	OCA N=168 n (%)	Placebo N=166 n (%)
Biochemical response, n (%)	17 (10%)	4 (2%)
Nonresponse, n (%)	151 (90%)	162 (98%)
Missing data at Month 12	42 (25%)	28 (17%)

Source: Statistical reviewer analysis using Applicant submitted dataset adeff.xpt.

Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment arm; n, number of subjects in specified population or group

8.3.8 Safety Analysis

Hepatic adverse events were assessed for safety differently from the primary efficacy endpoint, and were adjudicated as hepatic clinical outcomes. These events are defined as events included in the "Hepatic Disorders Standardized MedDRA Query" i.e., as defined in the SMQ. These excluded the

following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders.

Analyses were performed for the following hepatic events including signs of hepatic decompensation:

3. Death due to hepatic event (any hepatic TEAE with outcome of death)
4. MELD score ≥15 (MELD ≥15)
5. Liver transplant (any procedure or AE with a PT of "Liver and small intestine transplant", Liver transplant", or "Renal and liver transplant")
6. Ascites (any AE with a PT of "Ascites", "Bacterascites", "Biliary ascites", or"Hemorrhagic ascites")
7. Variceal bleed (any AE with a PT of "Gastric varices hemorrhage" or "Esophageal varices hemorrhage")
8. Hepatic encephalopathy (any AE with a PT of "Hepatic encephalopathy")
9. Spontaneous bacterial peritonitis (any AE with a PT of "Peritonitis bacterial")

8.3.8.1 Cause of Death in Trial 747-302

Table 32 lists the causes of death in the safety (overall population) in Trial 747-302.

Table 32. AEs Leading to Death, Safety Population, Trial 747-302

Preferred Term	Total-OCA PY=413.2 N=168 n/py (IR)	Total-Placebo PY=347.1 N=166 n/py (IR)	IR Difference (95% CI)
Any AE leading to death	16/425.7 (3.8)	12/355.7 (3.4)	0.4 (-2.5, 3.2)
Myocardial infarction	1/413.2 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Subarachnoid hemorrhage	1/413.2 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Lower respiratory tract infection	1/413.2 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Respiratory failure	1/413.3 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Acute respiratory failure	1/413.3 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Complications of transplanted liver	1/413.6 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Hepatic function abnormal	1/413.7 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Hepatic cirrhosis	1/413.8 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Subdural hematoma	1/414.3 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Colorectal cancer	1/415.8 (0.2)	0/347.1 (0)	0.2 (-0.9, 1.4)
Cardio-respiratory arrest	2/414.2 (0.5)	1/347.5 (0.3)	0.2 (-1.2, 1.5)
Hepatic encephalopathy	2/417.9 (0.5)	1/347.6 (0.3)	0.2 (-1.2, 1.5)
Sepsis	1/413.2 (0.2)	1/347.8 (0.3)	-0.0 (-1.4, 1.1)
Mesenteric hemorrhage	0/413.2 (0)	1/350 (0.3)	-0.3 (-1.6, 0.6)
Hepatic failure	0/413.2 (0)	1/348.7 (0.3)	-0.3 (-1.6, 0.6)
Hepatorenal syndrome	0/413.2 (0)	1/347.6 (0.3)	-0.3 (-1.6, 0.6)
Cytomegalovirus infection	0/413.2 (0)	1/347.6 (0.3)	-0.3 (-1.6, 0.6)
Cholangiocarcinoma	0/413.2 (0)	1/347.3 (0.3)	-0.3 (-1.6, 0.6)
Hepatocellular carcinoma	0/413.2 (0)	1/347.1 (0.3)	-0.3 (-1.6, 0.6)
Sarcopenia	0/413.2 (0)	1/347 (0.3)	-0.3 (-1.6, 0.6)
Multiple organ dysfunction syndrome	1/415 (0.2)	2/348.6 (0.6)	-0.3 (-1.9, 0.8)

Source: Source: adae.xpt; Software: R Treatment-emergent adverse events (TEAE) are defined as any event starting on or after the first dose of the investigational product till the end of study, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product until the end of study (on-study TEAE). Duration is up to 2196 days.
Risk difference (with 95% confidence interval) is shown between total treatment and placebo.
For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate (per 100 patient-years); N, number of subjects in treatment arm; n, number of subjects with adverse event; OCA, obeticholic acid; PY, patient-years (total exposure); py, patient-years (at risk)

8.3.8.2 Pruritus in Trial 747-302

Table 33. Trial 747-302: Pruritus USPI-Labeled Population

Variable	USPI-Labeled OCA n=81	USPI-Labeled Placebo n=68
Subjects with pruritus event (%)	67 (82.7%)	33 (48.5%)
Subjects with severe pruritus events	26 (32.1%)	9 (13.2%)
Pruritis leading to drug withdrawal	12 (14.8%)	2 (2.9%)
Any drug holiday	17 (21%)	4 (5.9%)
Requiring treatment for pruritis	42 (51.9%)	18 (26.5%)

Source: Applicant provided IR response Table R 15.1.2 and CDS analyst.

8.3.8.3 Treatment Emergent Adverse Events, Adverse Events Definitions

Verbatim terms were mapped to PT and SOC using MedDRA version 17.1 for Trial 747-302 and version 23.0 for Trial 747-401.

Treatment-emergent adverse events (TEAEs) are defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of IP, up to 30 days following permanent IP discontinuation.

Additional analyses were performed specifically for AE occurring after permanent IP discontinuation for subjects participating in follow-up via scheduled study visits, telephone calls, or electronic medical record review, defined as any AE with onset at least 30 days after permanent discontinuation of IP.

Hepatic adverse events assessment for safety were different from the primary efficacy endpoint, and were adjudicated as hepatic clinical outcomes. These events are defined as those included in the "Hepatic Disorders Standardized MedDRA Query (SMQ)."

8.3.8.4 Overview of Treatment Emergent Adverse Events (TEAE) in Trial 747-302

For the overall safety population, AE of any severity occurred more frequently in the subjects treated with OCA (incidence rate [IR] of 739.9 compared to 597.7 for placebo; IR difference of 142.1; 95% CI -2.2, 291.3) in Trial 747-302.

Imbalances were noted in AE leading to dose modification of OCA compared to placebo (IR 32.3 and 21.9; IR difference 10.4; 95% CI 1.6, 19.6), which was driven by AEs leading to reduction in study drug dose as the modification (Table 34).

The limitations to our assessment of AE in Trial 747-302 include discontinuations or early study closure, and the considerable amount of missing data during the trial.

Table 34. Overview of Treatment-Emergent Adverse Events, Safety Population, Study Trial 747-302

Event Category	Total OCA PY=413.2 N=168 n/py (IR)	Total Placebo PY=347.1 N=166 n/py (IR)	IR Difference (95% CI)
SAE	68/370.5 (18.4)	75/318.8 (23.5)	-5.2 (-12.3, 1.6)
SAEs with fatal outcome	15/425.7 (3.5)	11/355.2 (3.1)	0.4 (-2.4, 3.1)
Life-threatening SAEs	4/413.6 (1.0)	2/342.8 (0.6)	0.4 (-1.2, 2.0)
SAEs requiring hospitalization	67/368.1 (18.2)	70/321.7 (21.8)	-3.6 (-10.5, 3.1)
AE leading to permanent discontinuation of study drug	64/407.7 (15.7)	48/345.4 (13.9)	1.8 (-3.8, 7.3)
AE leading to dose modification of study drug	82/253.9 (32.3)	61/278.1 (21.9)	10.4 (1.6, 19.6) *
AE leading to reduction of study drug	45/322.7 (13.9)	23/316.2 (7.3)	6.7 (1.7, 12.0) *
Any AE	164/22.2 (739.9)	162/27.1 (597.7)	142.1 (-2.2, 291.3)
Severe and worse	93/313.7 (29.6)	86/306.1 (28.1)	1.6 (-7.0, 10.1)

Source: Source: adae.xpt; Software: R Treatment-emergent adverse events (TEAE) are defined as any event starting on or after the first dose of the investigational product till the end of study, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product till the end of study (on-study TEAE). Duration is up to 2196 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Severity as assessed by the investigator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Significant imbalance (CI excludes zero), potential safety signal/imbalance.

Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate (per 100 person-years); N, number of patients subjects in treatment arm; n, number of patients subjects with at least one event; OCA, obeticholic acid; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event

Table 35 displays AEs that occurred in the USPI-labeled and USPI-contraindicated populations. In the USPI-labeled population, SAEs with fatal outcomes, AEs leading to dose modification, dose reduction, any AE, and severe and worse AE occurred in larger numbers of OCA-treated compared to placebo-treated subjects.

Table 35. Overview of Treatment Emergent Adverse Events by USPI Labeled and Contraindicated Populations, Trial 747-302

	USPI-Labeled			USPI-Contraindicated		
Event Category	OCA PY=211.7 N=81 n/py (IR)	Placebo PY=142.9 N=68 n/py (IR)	IR Difference (95% CI)	OCA PY=201.6 N=87 n/py (IR)	Placebo PY=204.2 N=98 n/py (IR)	IR Difference (95% CI)
SAE	23/211.1 (10.9)	20/129.8 (15.4)	-4.5 (-13.7, 3.2)	45/159.4 (28.2)	55/188.9 (29.1)	-0.9 (-12.2, 10.8)
SAEs with fatal outcome	4/214.7 (1.9)	1/143.3 (0.7)	1.2 (-2.2, 4.2)	11/211 (5.2)	10/211.9 (4.7)	0.5 (-4.1, 5.2)
Life-threatening SAEs	1/211.7 (0.5)	0/142.9 (0)	0.5 (-2.2, 2.7)	3/201.9 (1.5)	2/199.8 (1.0)	0.5 (-2.3, 3.5)
SAEs requiring hospitalization	22/208.7 (10.5)	19/130.2 (14.6)	-4.1 (-13.0, 3.5)	45/159.4 (28.2)	51/191.5 (26.6)	1.6 (-9.4, 13.1)
Other	7/213.3 (3.3)	5/142.2 (3.5)	-0.2 (-5.2, 3.8)	19/206.2 (9.2)	20/206 (9.7)	-0.5 (-6.7, 5.7)
AE leading to permanent discontinuation of study drug	27/209 (12.9)	21/143.5 (14.6)	-1.7 (-10.4, 6.0)	37/198.7 (18.6)	27/201.9 (13.4)	5.3 (-2.6, 13.5)
AE leading to dose modification of study drug	34/144.7 (23.5)	23/120.3 (19.1)	4.4 (-7.2, 15.7)	48/109.3 (43.9)	38/157.8 (24.1)	19.9 (5.9, 35.7) *
AE leading to reduction of study drug	20/173.8 (11.5)	7/131.2 (5.3)	6.2 (-0.7, 13.1)	25/149 (16.8)	16/184.9 (8.7)	8.1 (0.6, 16.8) *
Any AE	77/13.4 (575.8)	65/14.1 (461.0)	114.8 (-55.8, 289.9)	87/8.8 (989.3)	97/13 (746.0)	243.3 (-5.3, 510.7)
Severe and worse	40/164.9 (24.3)	27/120.3 (22.4)	1.8 (-10.2, 13.1)	53/148.8 (35.6)	59/185.8 (31.8)	3.9 (-8.6, 16.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events (TEAE) are defined as any event starting on or after the first dose of the investigational product till the end of study, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product till the end of study (on-study TEAE).

Duration is up to 2196 days.

Risk difference (with 95% confidence interval) is shown between total treatment and placebo.

Severity as assessed by the investigator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Significant imbalance (CI excludes zero), potential safety signal/imbalance.

Abbreviations: AE, adverse event; CI, confidence interval; IR, incidence rate (per 100 person-years); N, number of patients subjects in treatment arm; n, number of patients subjects with at least one event; OCA, obeticholic acid; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event; USPI, United States Prescribing Information

8.3.9 Detection of OCA in the Placebo Arm

In the placebo arm, 40 subjects had at least one quantifiable PK sample. Thirty-five subjects in the placebo arm had OCA detected in plasma during the double-blind phase. The use of commercial OCA was reported for 10 subjects, but the other 25 subjects did not have a record of commercial OCA use. Eleven of twenty-five subjects had quantifiable PK samples before their last placebo drug administration, and two of them had OCA detected at multiple timepoints. One subject had one quantifiable PK sample at screening and four subjects had quantifiable PK samples in the follow-up phase. The reason for OCA exposure in subjects in Study 747-302 treated with OCA in the placebo arm was not fully documented.

8.3.10 Pharmacodynamics Results

Biochemical endpoints, including alkaline phosphatase (ALP) and total bilirubin (TB), were measured in Trial 302. At baseline, the mean ALP level was higher in the USPI-labeled subjects compared to the USPI-contraindicated subjects, and the mean TB level was lower in the USPI-labeled subjects than the USPI-contraindicated subjects.

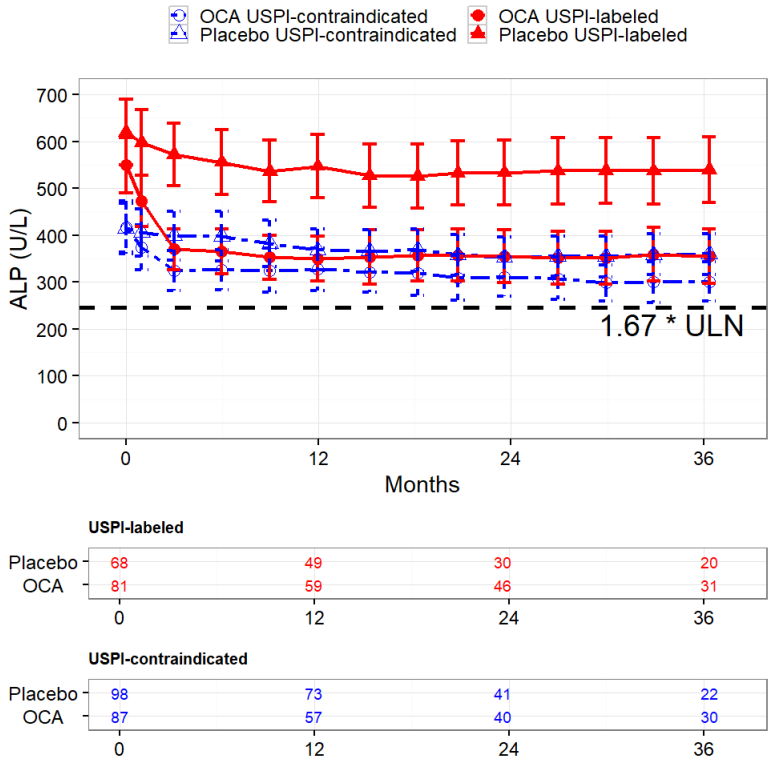
In USPI-labeled subjects, a greater mean ALP decrease was observed in those treated with OCA than placebo within 4 months of treatment (Figure 14) although the mean ALP level remained >1.67× ULN in both OCA- and placebo-treated subjects. The mean TB level slightly increased in the placebo-treated subjects and was stable in the OCA-treated subjects (Figure 15).

In USPI-contraindicated subjects, a slight decrease in mean ALP was observed in OCA-treated subjects compared with placebo treated subjects, and the mean ALP level was >1.67× ULN in both groups. The mean TB increased in placebo-treated subjects and was higher than that in OCA-treated subjects.

Of note, the mean ALP and TB levels are presented using the last observation carried forward (LOCF) method for missing data. There are limitations to the LOCF method of handling missing data; however, ignoring missing data is not appropriate because dropout could have been informed by biochemical results. Considering the high dropout rate in this study, data were presented only up to 36 months after randomization with imputation by LOCF.

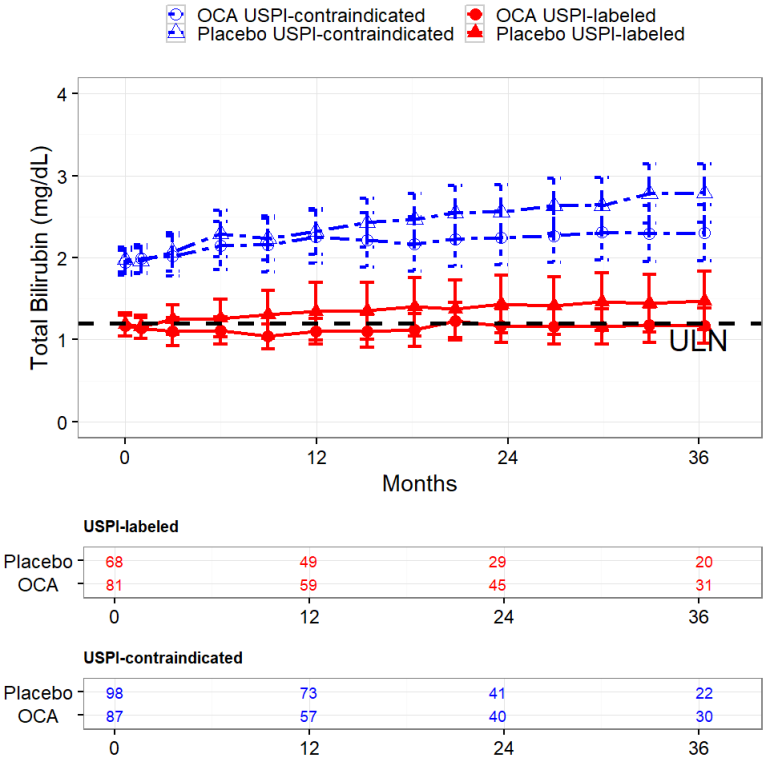
At Month 12, 10% and 2% of subjects in the OCA and placebo arms, respectively, in Trial 302 achieved the biochemical response (ALP <1.67× ULN, ALP reduction from baseline ≥15%, and TB ≤ULN). Refer to Section 4.1 The biochemical response rate at Month 12 in Trial 301 was 46% and 10% in the OCA-treated subjects and placebo-treated subjects, respectively, compared to a markedly lower biochemical response rate observed in Trial 747-302.

Figure 14. Mean (95% CI) of Alkaline Phosphatase (ALP) Over Time in Trial 302 (Last Observation Carried Forward)



Source: Reviewer's analysis based on adlb.xpt for Trial 302; table at bottom shows the number of observations without LOCF; there are limitations to the LOCF method of handling missing data; however, ignoring missing data is not appropriate because dropout could have been informed by biochemical results. Considering the high dropout rate in this trial, data were presented only up to 36 months after randomization with imputation by last observation carried forward.
Abbreviations: ULN, upper limit of normal; OCA, obeticholic acid; ALP, alkaline phosphatase

Figure 15. Mean (95% CI) of Total Bilirubin Over Time in Trial 302 (Last Observation Carried Forward)



Source: Reviewer's analysis on adlb.xpt for Trial 302; table at bottom shows the number of observations without LOCF; there are limitations to the LOCF method of handling missing data; however, ignoring missing data is not appropriate because dropout could have been informed by biochemical results. Considering the high dropout rate in this trial, data were presented only up to 36 months after randomization with imputation by last observation carried forward.
Abbreviations: ULN, upper limit of normal; OCA, Obeticholic Acid

8.4 Study 747-405 Additional Information

Table 36. Study 747-405: FDA's Tabular Summary of Study 747-405

Domain	Summary
Product	Obeticholic acid (OCA; OCALIVA®)
Therapeutic area	Hepatology
Indication	Adult PBC with no cirrhosis or compensated cirrhosis (without portal hypertension) – for use in combination with UDCA (for patients with inadequate UDCA response) or as monotherapy (for patients with intolerance to UDCA)
Regulatory purpose	To function as a confirmatory (pivotal) adequate and well-controlled study
Other evidence	Double-blind, placebo-controlled, 12-month RCT showing favorable treatment response (48% vs. 10%) on a surrogate endpoint reasonably likely to predict clinical benefit (ALP <1.67-fold ULN, TB ≤ULN, and ALP decrease by ≥15%)
Regulatory context	Low Tolerance for Uncertainty: RWE from Study 747-405 to function as principal support for traditional approval (clinical benefit confirmed) following accelerated (Subpart H) approval using a surrogate endpoint
Study objective	To estimate effect of OCA on time to first occurrence of death, liver transplantation, or hepatic decompensation in PBC patients with history of UDCA treatment
Study design	Observational cohort study

Domain	Summary
Time periods	Study Period: June 2015 to December 2021; Enrollment Period: June 2016 to December 2021
Design	Treatment Decision Design
Blinding	Not Applicable (RWD)
Data source	KOMODO claims linked (via DATAVANT) to commercial providers of laboratory services (LABCORP & QUEST), OPTN, SSDI, and Obituary Search
Study population	Inclusion criteria: • age ≥18 years • definite or probable PBC (≥1 inpatient claim or ≥2 outpatient claims on different dates) • UDCA-treatment failure (inadequate response, intolerance, or discontinuation) • ALP >121 U/L or TB >1.2 mg/dL • closed claims available for ≥12 months before index date (treatment start date or laboratory test date) Exclusion criteria: • concomitant liver disease • laboratory test indicators for hepatic decompensation or hepatobiliary injury (TB >3 mg/dL, ALP >10× ULN, ALT >10× ULN, AST >10× ULN) • history of malignancy, HIV, or liver transplantation • Paget's disease or recent bone fracture • previous treatment with OCA, fenofibrate, or bezafibrate • history of treatment with rifaximin and lactulose • pre-index hepatic decompensation event (e.g., variceal bleed, ascites, spontaneous bacterial peritonitis, hepatic hydrothorax, or hepatic encephalopathy)
Causal contrasts	As-Treated (Primary Analysis) and Intention to Treat (Exploratory Ad Hoc Analysis)
Exposure definition	OCA treatment identified by sequence of pharmacy dispensings with allowance for 90-day treatment gaps between dispensings and 90 days added to last dispensing in sequence
Comparator definition	Untreated comparator defined as follow-up without OCA treatment after instances of laboratory test abnormality (ALP >121 U/L or TB >1.2 mg/dL) that fulfill criteria for UDCA failure
Outcome definition	Death (KOMODO linked to SSDI or Obituary Search), Liver Transplantation (KOMODO linked to OPTN or KOMODO claims profile adjudicated as liver transplantation), or Hepatic Decompensation Event (KOMODO hospital record with diagnostic coding for (a) variceal bleeding – ICD-10 I85.01 or I85.11, (b) ascites – ICD-10 K65.2, K70.11, K70.31, K71.51, R18.0, R18.8, or J94.8, or (c) hepatic encephalopathy – ICD-10 B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, G93.40, K70.41, K72.01, K72.11, K72.90, or K72.91)
Covariates	Measured: (a) COVID-19 time period (2016-2019 or 2020-2021), (b) sex, (c) age, (d) insurance type, (e) months since first UDCA failure, (f) UDCA treatment status on index date, (g) cirrhosis, (h) portal hypertension, (i) Charlson Comorbidity Score, (j) ALP, (k) TB, (l) ALT, (m) AST, and (n) platelet count
Start (index) date	(a) treated (exposed) index date identified by new OCA dispensing and (b) OCA-untreated (unexposed or control) index dates identified by qualified laboratory test dates showing ALP >121 U/L or TB >1.2 mg/dL. See **FOOTNOTE**.

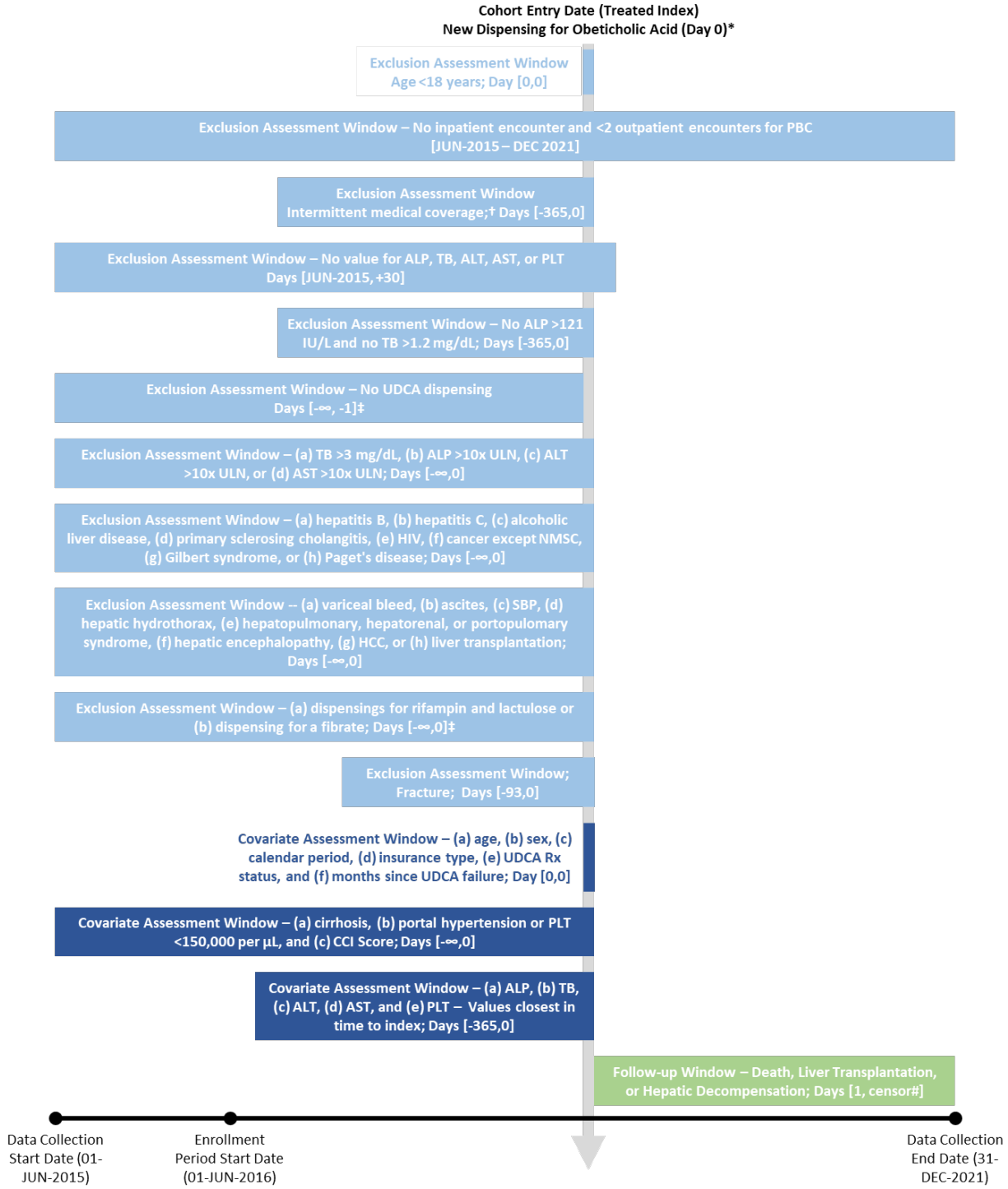
Domain	Summary
As-treated end date	(a) death, (b) liver transplantation, (c) hepatic decompensation event, (d) study end date (31-DEC-2021), (e) health insurance end date, (f) fibrate start date, (g) OCA end date (applicable to follow-up periods identified by new OCA dispensing), (h) OCA start date (applicable to OCA-untreated follow-up), or (i) UDCA treatment episode start date (applicable to OCA-untreated follow-up fulfilling UDCA discontinuation criteria)
Statistical method	SMR-weighted Cox regression (SMRs updated for each index) with 95% confidence intervals estimated by nonparametric bootstrapping method
Sample size	Planned: N≥395 treated patients and N≥5,916 control patients; 80% power (α=0.05, 2-sided; expected hazard ratio=0.5) for outcome with 6% event rate in control patients (assuming moderate confounding) Achieved: N=4,758 patients overall including N=432 OCA exposed
Confounder control	SMR weighting
Missing data method	Cox regression analyses used patient indexes with complete covariate data (i.e., missing data not imputed)

Source:

Footnote**:** The Treatment Decision Design allows patients to contribute (1) one treated index only, (2) one or more OCA-untreated (control) indexes, or (3) one or more OCA-untreated (control) indexes as well as one OCA-treated index as long as all OCA-untreated (control) indexes precede the OCA-treated index.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OPTN, Organ Procurement and Transplantation Network; PBC, primary biliary cholangitis; RCT, randomized clinical trial; RWD, real-world data; RWE, real-world evidence; SMR, standardized morbidity ratio; SSDI, Social Security Death Index; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Figure 16. Study 747-405: Graphical Summaries of Design of Study 747-405 (Treated)

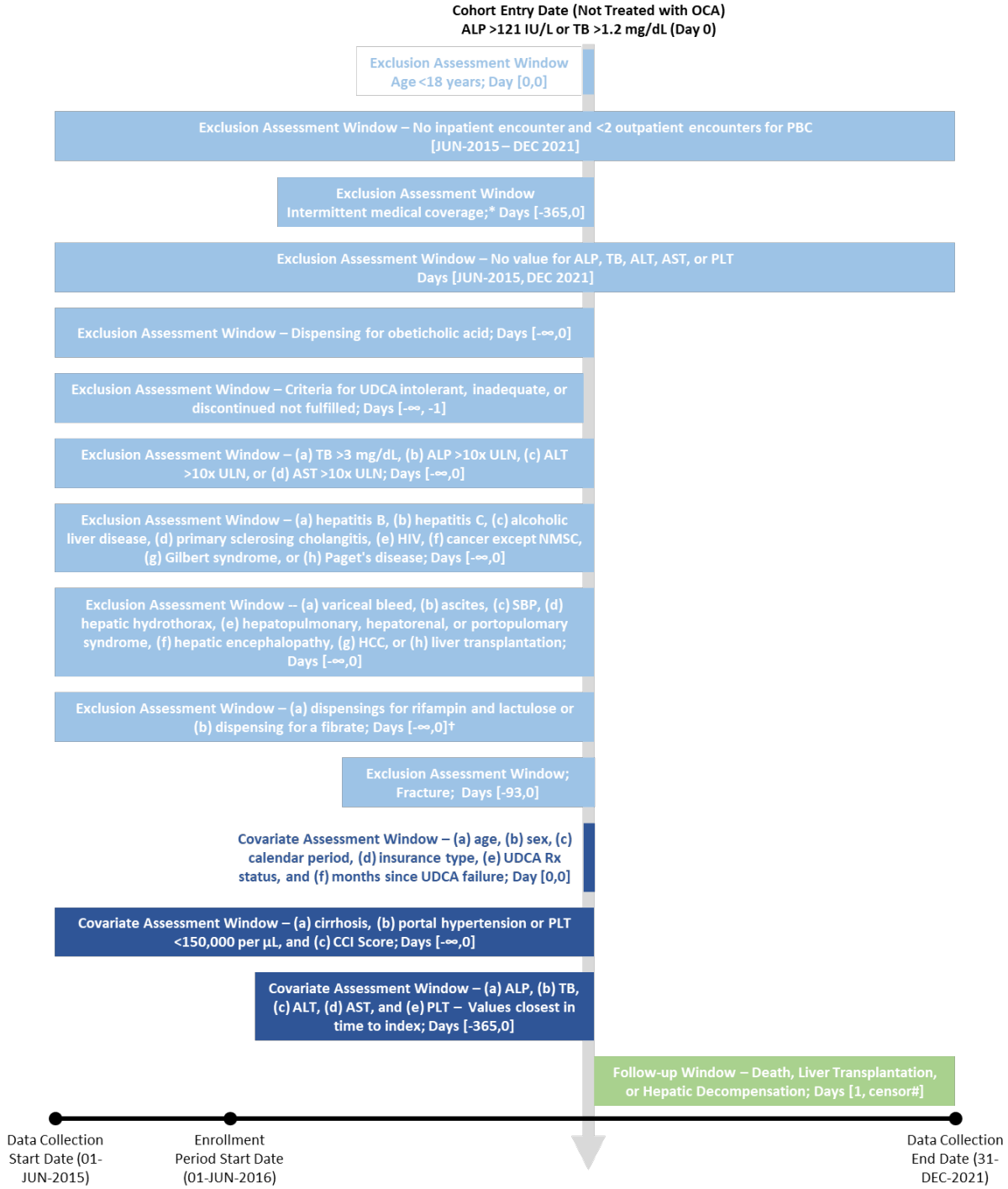


Source: Generated by the Clinical Reviewer.

Footnotes: * First dispensing for obeticholic acid during the Enrollment Period; † Permitting 62-day coverage gaps; ‡ No UDCA-treatment episode with end date on or after June 1, 2015 and start date before Cohort Entry Date; # Follow-up censored on (a) study end date (31-DEC-2021), (b) medical coverage end date, (c) fibrate start date, or (d) OCA end date

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; HCC, hepatocellular carcinoma; NMSC, non-melanoma skin cancer; PBC, primary biliary cholangitis; PLT, platelet count; Rx, treatment; SBP, spontaneous bacterial peritonitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Figure 17. Study 747-405: Graphical Summaries of Design of Study 747-405 (Control)



Source: Generated by the Clinical Reviewer.

* Permitting 62-day coverage gaps; † Treatment episode end date on or after 01-JUN-2015; # Follow-up censored on (a) study end date (December 31, 2021), (b) medical coverage end date, (c) fibrate start date, (d) OCA treatment episode start date, or (e) UDCA treatment episode start date (applicable to follow-up periods identified by laboratory test abnormalities that fulfill UDCA discontinuation criteria).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; HCC, hepatocellular carcinoma; NMSC, nonmelanoma skin cancer; PBC, primary biliary cholangitis; PLT, platelet count; Rx, treatment; SBP, spontaneous bacterial peritonitis; TB, total bilirubin; UDCA, ursodeoxycholic acid; ULN, upper limit of normal

Table 37. Study 747-405: Covariates Used by Study 747-405 for Statistical Adjustment

Assessment Method and Variable Name	Variable Definition
Fixed	
Gender	Binary (female, male)
Updated on index date	
Calendar time period	Binary (2016-2020, 2020-2021)
Age	Discrete integer year
Health insurance type	Six categories[1]
Months since first ursodeoxycholic acid (UDCA) failure	Continuous
On UDCA	Binary
Assessed over [-∞,0]-day pre-index period[2]	
Cirrhosis[3]	Binary
Clinical evidence of portal hypertension[4]	Binary
Charlson Comorbidity Index	Discrete integer score (0 to 18)
Most recent value in [-365,0]-day pre-index period	
Alkaline phosphatase (ALP)	Continuous (IU/L)[5]
Total bilirubin (TB)	Continuous (mg/dL)
Alanine aminotransferase (ALT)	Continuous (IU/L)
Aspartate aminotransferase (AST)	Continuous (IU/L)
Platelet count	Continuous (10,000/µL)

Source: Generated by the Clinical Reviewer.

[1] Commercial, Self-insured/Exchanges, Medicare, Medicaid, Dual-eligible, and Other.

[2] June 1, 2015 (study start) through index date (inclusive).

[3] Identified by (a) encounter claim with ICD-9 571.5 (Cirrhosis of liver without mention of alcohol), ICD-10 K74.5 (Biliary cirrhosis, unspecified), ICD-10 K74.60 (Unspecified cirrhosis of liver), or ICD-10 K74.69 (Other cirrhosis of liver) and (b) liver imaging or biopsy procedure in preceding 6 months.

[4] Identified by (a) encounter claim with ICD-9 456.1 (Esophageal varices without mention of bleeding), ICD-9 456.21 (Esophageal varices in diseases classified elsewhere, without mention of bleeding), ICD-9 456.8 (Varices of other sites), ICD-9 572.3 (Portal hypertension), ICD-10 K76.6 (Portal hypertension), ICD-10 I85.00 (Esophageal varices without bleeding), ICD-10 I85.10 (Secondary esophageal varices without bleeding), or ICD-10 I86.4 (Gastric varices) or (b) platelet count <150,000 per µL.

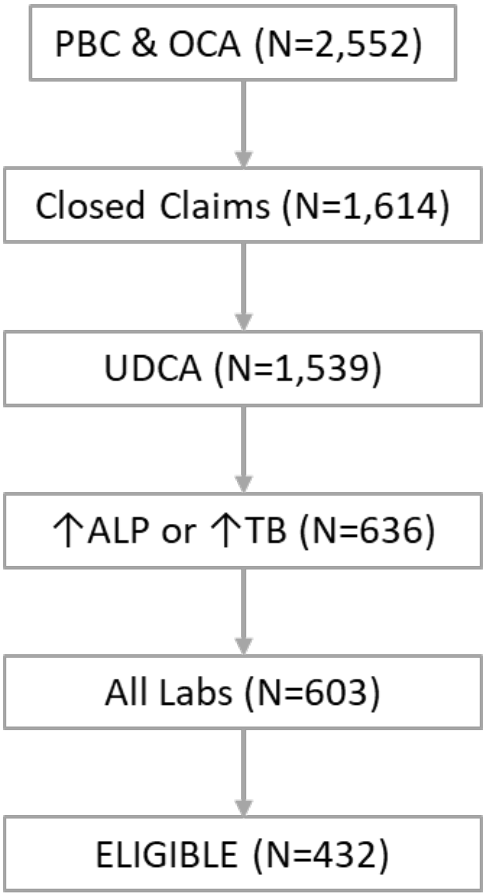
[5] Linear and squared terms.

8.4.1 Patient Attrition Leading to OCA-Treated Group, Study 747-405

Study 747-405 identified 2,552 unique patients in KOMODO with (a) age ≥18 years, (b) ≥1 OCA dispensing during the enrollment period (June 1, 2016 to December 31, 2021), and (c) encounter claims that fulfilled the criteria for PBC. Figure 18 summarizes the subsequent attrition that resulted in an OCA-treated group. Study 747-405 excluded (in sequence):

- 938 (36.8%) of 2,552 patients for closed claims not available during 12-month preindex period.
- 75 (4.6%) of 1,614 patients with closed claims but no evidence for UDCA use during preindex period.
- 903 (58.7%) of 1,539 patients with closed claims and UDCA but missing or normal values for ALP and TB (assessed during [-365,0]-day preindex period).
- 33 (5.2%) of 636 patients with closed claims, UDCA, and elevated ALP or TB but missing value for ALP, TB, AST, ALT, or PLT (assessed during [-365,0]-day preindex period).
- 171 (28.4%) of 603 otherwise eligible patients because of disqualifying pre-index concomitant disease, liver disease complication, bone fracture, drug treatment, or laboratory test abnormality.

Figure 18. Patient Attrition Leading to an OCA-Treated Group for Study 747-405



Source: Epidemiology Review of Study 747-405.

Table 38 summarizes the baseline characteristics of all adult OCA-treated PBC patients in KOMODO before and after application of the five filters used to determine study eligibility.

Table 38. Baseline Characteristics for All PBC Patients in KOMODO With Age ≥18 Years at First OCA Dispensing, Before and After Sequential Application of Five Eligibility Filters, Study 747-405.

	PBC & OCA		Closed Claims		UDCA		↑ALP or ↑TB		All Labs		No Exclusions	
	N=2,552		N=1,614		N=1,539		N=636		N=603		N=432	
Baseline Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex												
Female	2,336	91.5	1,470	91.1	1,403	91.2	579	91.0	548	90.9	396	91.7
Male	216	8.5	144	8.9	136	8.8	57	9.0	55	9.1	36	8.3
Age, years												
18-34	62	2.4	46	2.9	44	2.9	16	2.5	14	2.3	8	1.9
35-44	257	10.1	166	10.3	160	10.4	66	10.4	62	10.3	45	10.4
45-54	660	25.9	455	28.2	438	28.5	187	29.4	177	29.4	126	29.2
55-64	950	37.2	623	38.6	599	38.9	247	38.8	235	39.0	175	40.5
65-74	485	19.0	247	15.3	228	14.8	91	14.3	87	14.4	60	13.9
75-89	138	5.4	77	4.8	70	4.5	29	4.6	28	4.6	18	4.2
Year												
2016	331	13.0	225	13.9	215	14.0	75	11.8	68	11.3	46	10.6
2017	610	23.9	407	25.2	383	24.9	143	22.5	132	21.9	97	22.5
2018	373	14.6	245	15.2	230	14.9	96	15.1	93	15.4	67	15.5
2019	484	19.0	295	18.3	283	18.4	130	20.4	122	20.2	84	19.4
2020	371	14.5	207	12.8	200	13.0	79	12.4	76	12.6	59	13.7
2021	383	15.0	235	14.6	228	14.8	113	17.8	112	18.6	79	18.3
Cirrhosis												
Recorded	1,171	45.9	812	50.3	781	50.7	337	53.0	324	53.7	214	49.5
Not recorded	1,381	54.1	802	49.7	758	49.3	299	47.0	279	46.3	218	50.5
Portal Hypertension												
Recorded	584	22.9	377	23.4	360	23.4	196	30.8	192	31.8	99	22.9
Not recorded	1,968	77.1	1,237	76.6	1,179	76.6	440	69.2	411	68.2	333	77.1
CCI Score												
0 to 1	830	32.5	483	29.9	460	29.9	176	27.7	166	27.5	142	32.9
2 to 3	784	30.7	504	31.2	481	31.3	187	29.4	178	29.5	148	34.3
4 to 6	635	24.9	413	25.6	395	25.7	174	27.4	167	27.7	98	22.7
7 to 10	251	9.8	174	10.8	165	10.7	81	12.7	74	12.3	39	9.0
>10	52	2.0	40	2.5	38	2.5	18	2.8	18	3.0	5	1.2

Source: Epidemiology Review of Study 747-405.

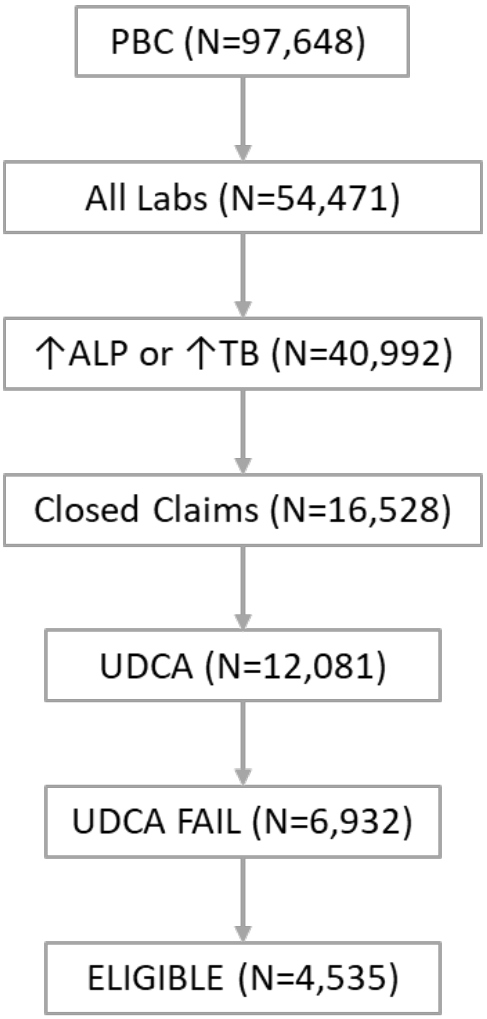
Abbreviations: ALP, alkaline phosphatase; CCI, Charlson Comorbidity Index; OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid

8.4.2 Patient Attrition Leading to OCA-Untreated (Control) Group, Study 747-405

Study 747-405 identified 97,648 unique patients in KOMODO with encounter claims that fulfilled criteria for PBC. Figure 19 summarizes subsequent attrition leading to a control group. Specifically, Study 747-405 excluded (in sequence):

- 43,177 (44.2%) of 97,648 patients for missing laboratory data.
- 13,479 (24.7%) of 54,471 patients without elevated ALP (>121 U/L) or TB (>1.2 mg/dL) recorded in the enrollment period (June 2016 to December 2021).
- 24,464 (59.7%) of 40,992 patients without elevated ALP or TB preceded by a ≥365-day period of closed claims.
- 4,447 (26.9%) of 16,528 patients with no evidence for UDCA use before any closed ALP or TB elevation.
- 5,149 (42.6%) of 12,081 patients for UDCA not meeting the failure criteria (intolerance, inadequacy, or discontinuation).
- Finally, Study 747-405 excluded 2,397 (34.6%) of 6,932 patients because concomitant disease, liver disease complication, bone fracture, drug treatment, or laboratory test abnormality disqualified every candidate index.

Figure 19. Patient Attrition Leading to a Control Group for Study 747-40



Source: Study 747-405 CSR, Figure 6.

Table 39 summarizes the baseline characteristics assigned to the earliest index for (a) control patients enrolled in Study 747 405 and (b) a sample of excluded (screen-failure) PBC patients in KOMODO with nonmissing ALP or TB (June 2016 to December 2021), before and after sequential application of the four filters used to determine study eligibility. The base population for Table 39 excludes patients with any OCA dispensing during the enrollment period (June 1, 2016 to December 31, 2021).

Table 39. Baseline Characteristics Assigned to the Earliest Index for (a) Control Patients Enrolled in Study 747-405 and (b) a Sample of Excluded (Screen-Failure) PBC Patients in KOMODO With Nonmissing ALP or TB (June 2016 to December 2021), Before and After Sequential Application of Four Eligibility Filters, Study 747-405

			Screen Failure									
	Enrolled		Any ALP/TB in PBC		Closed Claims		Any UDCA		↑ALP/↑TB All Labs		UDCA Fail	
	N=4,326		N=6,592		N=2,603		N=1,304		N=523		N=303	
Baseline Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex												
Female	3,903	90.2	5,492	83.3	2,120	81.4	1,135	87.0	544	83.4	243	80.2
Male	423	9.8	1,100	16.7	483	18.6	169	13.0	108	16.6	60	19.8
Age, years												
18-34	95	2.2	232	3.5	132	5.1	61	4.7	41	6.3	17	5.6
35-44	281	6.5	475	7.2	221	8.5	108	8.3	46	7.1	25	8.3
45-54	819	18.9	1,070	16.2	510	19.6	234	17.9	124	19.0	52	17.2
55-64	1,653	38.2	1,849	28.0	920	35.3	477	36.6	230	35.3	106	35.0
65-74	936	21.6	1,901	28.8	543	20.9	283	21.7	136	20.9	64	21.1
75-89	542	12.5	1,065	16.2	277	10.6	141	10.8	75	11.5	39	12.9
Year												
2016	459	10.6	2,075	31.5	619	23.8	198	15.2	83	12.7	25	8.3
2017	793	18.3	1,878	28.5	684	26.3	265	20.3	123	18.9	56	18.5
2018	791	18.3	1,020	15.5	488	18.7	220	16.9	108	16.6	48	15.8
2019	768	17.8	776	11.8	350	13.4	218	16.7	99	15.2	55	18.2
2020	731	16.9	466	7.1	228	8.8	179	13.7	107	16.4	56	18.5
2021	784	18.1	377	5.7	234	9.0	224	17.2	132	20.2	63	20.8
Cirrhosis												
Recorded	1,589	36.7	1,383	21.0	782	30.0	541	41.5	337	51.7	194	64.0
Not recorded	2,737	63.3	5,209	79.0	1,821	70.0	763	58.5	315	48.3	109	36.0
Portal Hypertension												
Recorded	941	21.8	1,627	24.7	725	27.9	398	30.5	287	44.0	175	57.8
Not recorded	3,385	78.2	4,965	75.3	1,878	72.1	906	69.5	365	56.0	128	42.2
CCI Score												
0 to 1	1,262	29.2	3,361	51.0	1,137	43.7	474	36.3	190	29.1	75	24.8
2 to 3	1,501	34.7	1,316	20.0	508	19.5	283	21.7	115	17.6	30	9.9
4 to 6	1,051	24.3	1,194	18.1	545	20.9	321	24.6	195	29.9	96	31.7
7 to 10	429	9.9	553	8.4	297	11.4	159	12.2	104	16.0	66	21.8
>10	83	1.9	168	2.5	116	4.5	67	5.1	48	7.4	36	11.9

Source: Epidemiology Review of Study 747-405.

Abbreviations: ALP, alkaline phosphatase; CCI, Charlson Comorbidity Index; OCA, obeticholic acid; PBC, primary biliary cholangitis; TB, total bilirubin; UDCA, ursodeoxycholic acid

8.4.3 Methods Used by Study 747-405 to Identify Treatment-Emergent Adverse Events of Special Interest (AESI)

Study 747-405 identified adverse events using ICD-9 and ICD-10 diagnosis codes attached to medical encounters aggregated by KOMODO. For data analysis and presentation, Study 747-405 created a lookup file that mapped each ICD code to a MedDRA preferred term.

Study 747-405 defined a TEAE as an adverse event observed during follow-up if (a) not observed during the entire pre-index period or (b) observed during the pre-index period but then observed in a worsened state during follow-up. Study 747-405 defined worsening "as an event associated with a hospitalization or death when there was no history of hospitalization for the event pre-index" (Study 747-405 CSR, p. 52). Study 747-405 defined safety follow-up as (a) time from index date to OCA end date for OCA-treated periods and (b) time from index date to OCA start date or end to closed claims for OCA-untreated periods.

Study 747-405 used the codes summarized in Table 40 to define pruritus as an AESI.

Table 40. Code Map for Pruritus Adverse Event of Special Interest (AESI)

International Classification of Diseases (ICD)		MedDRA	
Code	**Description**	**Code**	**Term**
ICD-9 698	Pruritus and related conditions	10037087	Pruritus
ICD-9 698.0	Pruritus ani	10068172	Anal pruritus
ICD-9 698.1	Pruritus of genital organs	10037093	Pruritus genital
ICD-9 698.2	Prurigo	10037083	Prurigo
ICD-9 698.8	Other specified pruritic conditions	10037087	Pruritus
ICD-9 698.9	Unspecified pruritic disorder	10037087	Pruritus
ICD-10 L28.2	Other prurigo	10037083	Prurigo
ICD-10 L29.0	Pruritus ani	10068172	Anal pruritus
ICD-10 L29.1	Pruritus scroti	10037093	Pruritus genital
ICD-10 L29.2	Pruritus vulvae	10056530	Vulvovaginal pruritus
ICD-10 L29.3	Anogenital pruritus, unspecified	10037093	Pruritus genital
ICD-10 L29.8	Other pruritus	10037087	Pruritus
ICD-10 L29.9	Pruritus, unspecified	10037087	Pruritus

Source: STDM AE; Analysis Data Reviewer's Guide
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities

Table 41 shows the MedDRA terms used to define five AESIs other than pruritus.

Table 41. MedDRA Terms Used to Define Five Adverse Events of Special Interest

Adverse Event of Special Interest (AESI)	MedDRA Definition
Hepatic	PT in [Hepatic disorders (SMQ) or Drug related hepatic disorders – comprehensive search (SMQ)] but not in [Congenital, familial, neonatal and genetic disorders of the liver (SMQ), Liver infections (SMQ), Hepatic disorders specifically reported as alcohol-related (SMQ), or Pregnancy-related hepatic disorders (SMQ)]
Dyslipidemia	PT in Dyslipidemia (SMQ)
Cholecystitis/Cholelithiasis	[Biliary abscess, Biliary sepsis, Biliary tract infection, Gallbladder abscess, Gallbladder empyema, Bile duct necrosis, Bile duct obstruction, Bile duct stenosis, Biliary colic, Cholangitis, Cholangitis acute, Cholangitis chronic, Cholecystocholangitis, or Perforation bile duct] or PT in [Gallbladder Related Disorders (narrow SMQ) or Gallstone Related Disorders (narrow SMQ)]

Adverse Event of Special Interest (AESI)	MedDRA Definition
Renal	PT in [Acute Renal Failure (SMQ), Chronic Kidney Disease (SMQ), Proteinuria (SMQ), Renovascular disorders (SMQ), or Tubulointerstitial disease (SMQ)]
Cardiovascular	PT in [Embolic and thrombotic events (broad SMQ), Ischemic heart disease (broad SMQ), or Central nervous system vascular disorders (narrow SMQ)]

Source: Analysis Data Reviewer's Guide, p. 20

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, Standardized MedDRA Query

Study 747-405 CSR presented (a) SMR-weighted counts of OCA-treated and OCA-untreated patient units with ≥1 TEAE and (b) expressed incidence as the SMR-weighted number of patient units with ≥1 TEAE per 100 PY with 95% CI calculated by a generalized estimating equation model (Poisson distribution and log link function, treatment group covariate, and log(time at risk) as offset).

8.4.4 Study 747-405: QBA for Outcome Misclassification

Study 747-405 used similar diagnosis codes to both define a study population and identify hepatic decompensation events. FDA speculated that factors determining study eligibility and treatment group assignment might have led to nonequivalence between OCA-treated and untreated groups with respect to underlying liver disease (PBC or other cholestatic disease) and history of hepatic decompensation.

To address concern about nonequivalence between OCA-treated and -untreated groups, FDA conducted a QBA to assess the impact of differential false coding of hepatic compensation in compensated patients admitted to hospital during follow-up (Matthew P. Fox 2021). QBA Scenario #1 modeled the impact of differential false coding in OCA-treated and untreated groups with equal probability (post-SMR weighting) of hospital admission in a compensated state. QBA Scenario #2 assumed an untreated group with a two-fold higher probability of hospital admission in a compensated state.

Results from QBA indicate that two- to three-fold greater false coding in an untreated group might produce an apparent 20% to 40% treatment benefit in the absence of true benefit from OCA.

Table 42. Parameters Used to Quantify Bias From Outcome Misclassification

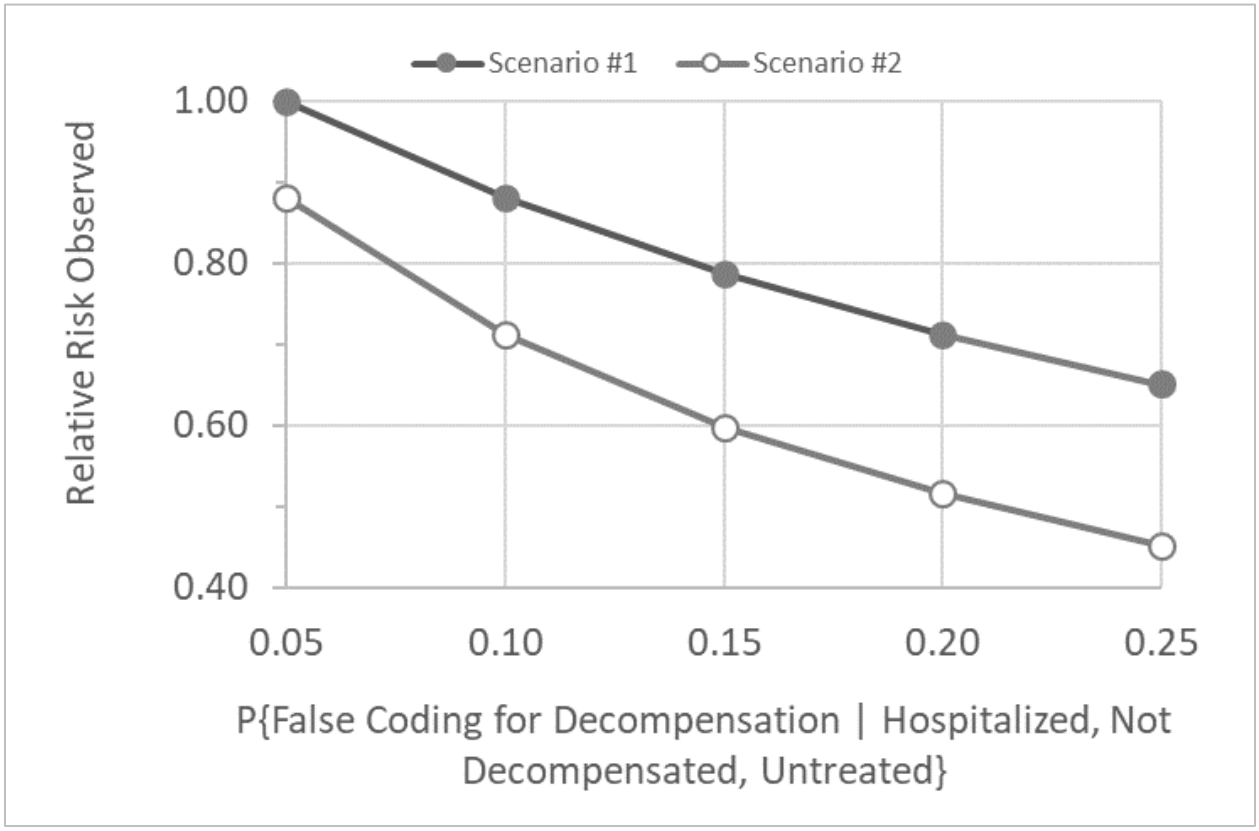
		Untreated	
QBA Parameter	Treated	Scenario #1	Scenario #2
P[Decompensation]	0.025	0.025	0.025
P[Hospitalization | Decompensation]	0.90	0.90	0.90
P[Hospitalization | No Decompensation]	0.05	0.05	0.10
P[Decompensation Coding | Hospitalized, Decompensation][1]	0.70	0.70	0.70
P[Decompensation Coding | Hospitalized, No Decompensation][2]	0.05	0.05-0.25	0.050-0.25

Source: Generated by Epidemiology Reviewer

[1] Sensitivity of inpatient diagnosis codes for hepatic decompensation.

[2] False coding rate (1- specificity).

Figure 20. QBA for Outcome Misclassification, Outcome Relative Risk Observed in Absence of True Benefit



Source: Generated by Epidemiology Reviewer

Expected Risk in Each Group Calculated by Equation: P[Decompensation] ×·P[Hospitalization | Decompensation] × P[Coded | Hospitalized, Decompensation] + (1-P[Decompensation]) ×·P[Hospitalization | No Decompensation] × P[Coded | Hospitalized, No Decompensation]