



Ocaliva® (Obeticholic Acid, OCA) Intercept Pharmaceuticals Inc.

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
September 13, 2024

FDA Introductory Remarks

Ruby Mehta, MD

Team Leader

Division of Hepatology and Nutrition (DHN)

Office of New Drugs

CDER, FDA



Primary Biliary Cholangitis

- Primary Biliary Cholangitis (PBC)
 - Rare, slowly progressive, immune-mediated, cholestatic chronic liver disease, with destruction of small bile ducts leading to liver damage
 - Predominantly affects middle-aged women (6:1 to 9:1)
 - Progression can lead to cirrhosis and portal hypertension; complications may lead to liver transplantation or death



Treatment for PBC

- FDA approved treatment
 - Ursodeoxycholic acid (UDCA) (Traditional Approval)
 - Second-line therapies (Accelerated Approval, using RLSE - ALP and TB)
 - Ocaliva® (obeticholic acid) (2016)
 - Elafibranor (2024)
 - Seladelpar (2024)
- Off-label treatment
 - Fibrates
- Unmet medical need
 - UDCA non-responders (~40% population); Symptomatic patients (e.g., pruritus, fatigue)

RLSE, reasonably likely surrogate endpoint; ALP, alkaline phosphatase; TB, total bilirubin

Obeticholic Acid (OCA)

- Ocaliva[®] (obeticholic acid, or OCA)
 - Synthetic derivative of chenodeoxycholic acid (6 α -ethyl-chenodeoxycholic acid)
- OCA is a Farnesoid X receptor (FXR) agonist
 - Reduces bile acid biosynthesis
 - Postulated to be anti-inflammatory and anti-fibrotic effects
 - Less polar than endogenous bile acids



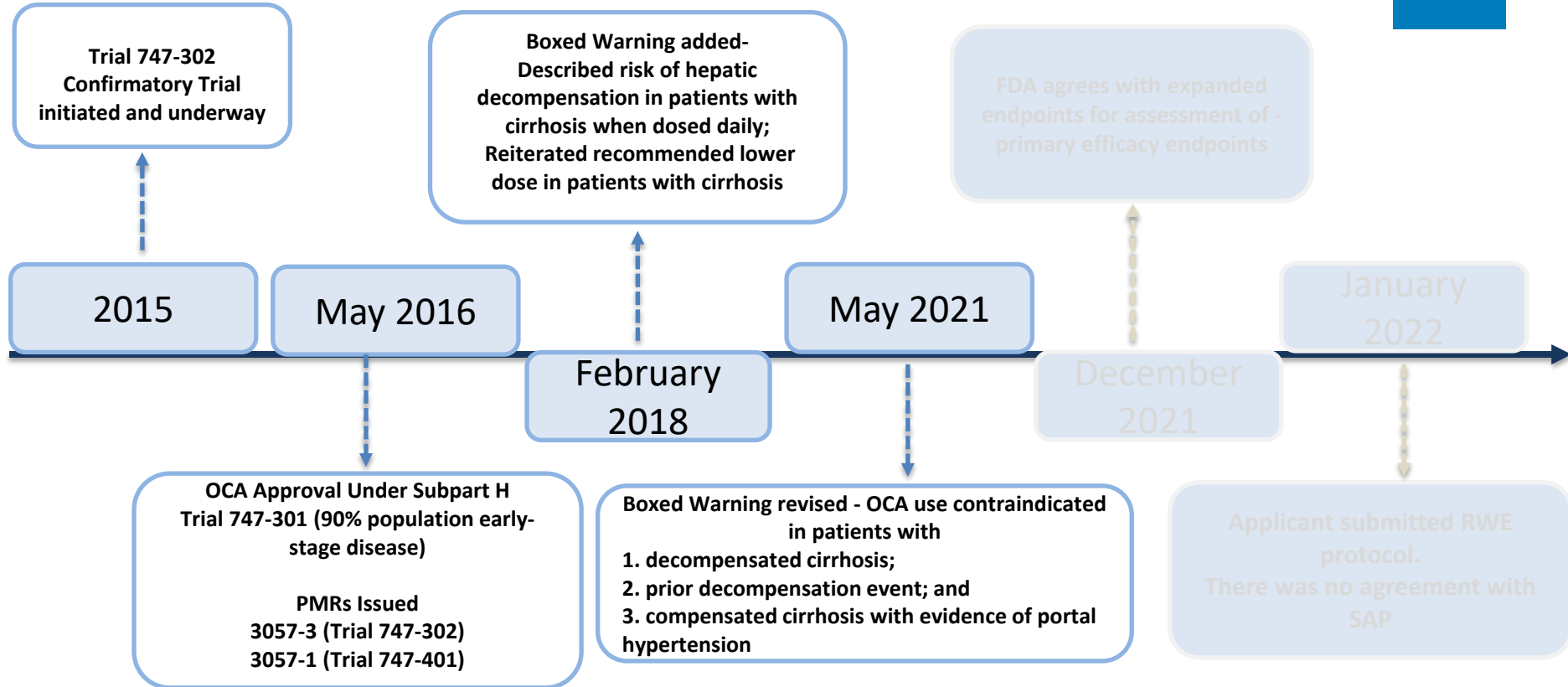
Regulatory Framework for Drug Approval

- Traditional Approval
 - A clinical endpoint—how a patient feels, functions, or survives (i.e., reduced mortality)
 - A validated surrogate endpoint (e.g., systolic blood pressure, hemoglobin A1c)
- Accelerated Approval (AA)
 - Intended to facilitate and expedite development and review of new drugs to fill an unmet medical need for a serious or life-threatening condition
 - Based on a surrogate endpoint that is “reasonably likely to predict clinical benefit”*; for drug development in PBC, FDA has agreed on ALP and TB as a surrogate endpoint
 - Because of remaining uncertainties in clinical benefit associated with drugs approved under AA, FDA requires that Sponsors conduct a confirmatory trial to verify and describe the clinical benefit
 - Drug approval can be withdrawn if the trial fails to verify the clinical benefit#
 - Newer expedited procedures for withdrawing approval have been provided by legislation^

*Section 506(c)(1) of the Federal Food, Drug, and Cosmetic (FDC) Act #Section 506(c)(3) of the FDC Act.

[^H.R.2617 - 117th Congress \(2021-2022\): Consolidated Appropriations Act, 2023 | Congress.gov | Library of Congress](#)

Regulatory History



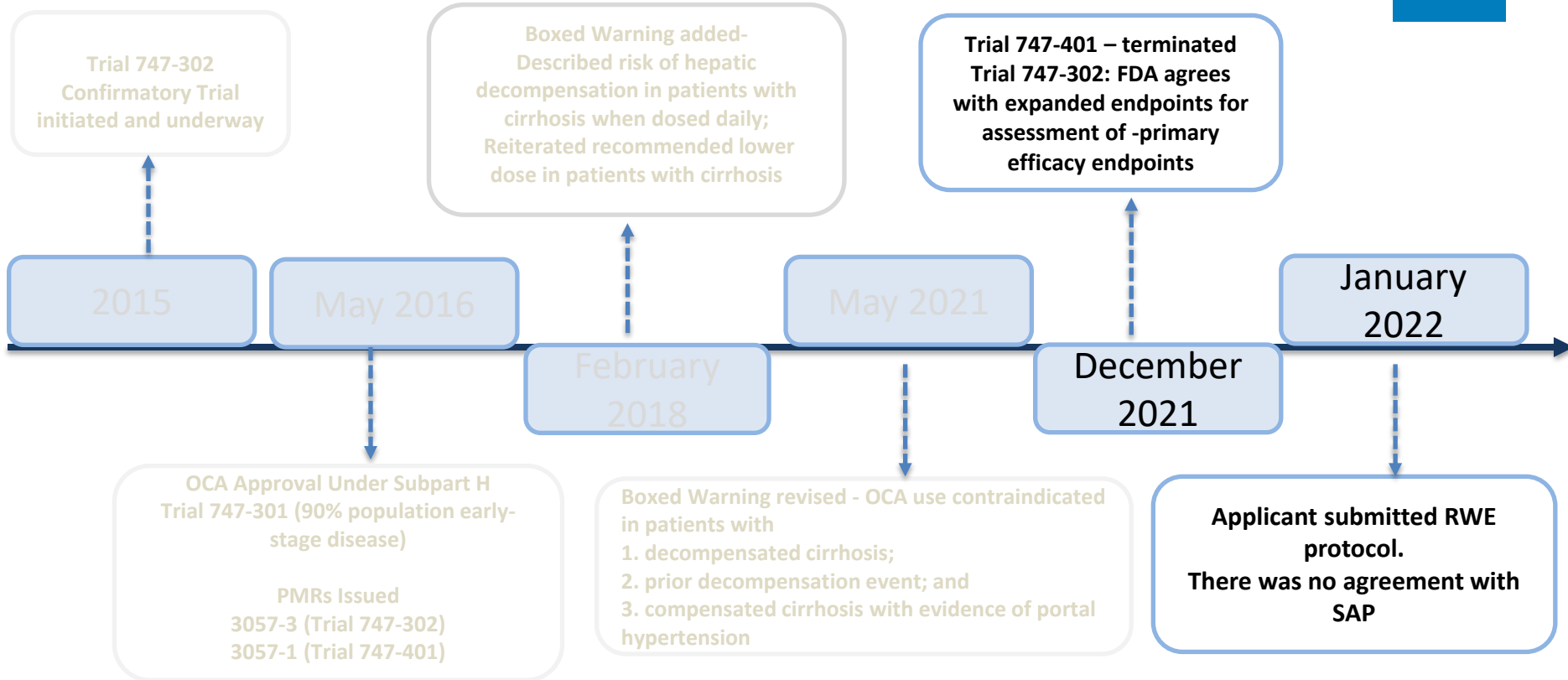
Safety Labeling Changes



- **February 2018:** Boxed warning to reiterate lower dose in patients with decompensated cirrhosis.
- FDA identified 25 cases of serious liver injury from the FDA Adverse Event Reporting System (FAERS) and published medical literature describing liver injury leading to liver decompensation event or failure in patients with cirrhosis.
- **May 2021:** Contraindication for patients with decompensated cirrhosis, a prior decompensation event, or compensated cirrhosis with evidence of portal hypertension; Boxed Warning and other sections of labeling revised.*
- Subsequent actions:
 - Trial 747-401: terminated because all trial subjects now contraindicated.
 - Trial 747-302: expanded endpoints agreed upon to accrue more events because 55% of enrolled subjects were now contraindicated.

*<https://www.fda.gov/drugs/drug-safety-and-availability/due-risk-serious-liver-injury-fda-restricts-use-ocaliva-obeticholic-acid-primary-biliary-cholangitis>

Regulatory History



OCA Clinical Program

Study 747-302 and Study 747-405

Study 747-302 (Confirmatory Trial)

- Randomized, double-blind, placebo-controlled trial
- Time-to-event driven trial powered to accrue 127 primary endpoints
- Non-cirrhotic, Child Pugh (CP) A, and CP B subjects with PBC randomized 1:1 to OCA or placebo arm
- Composite primary endpoint events
 - death (all-cause), liver transplant, Model for End-Stage Liver Disease (MELD) ≥ 15 , uncontrolled ascites, hospitalization due to variceal bleeding, hepatic encephalopathy (HE) (grade 2 and above), spontaneous bacterial peritonitis (SBP)
- The expanded endpoints were agreed upon in December 2021

Study 747-405 (Real-World Evidence Study)

- Observational study using administrative claims linked to
 - LabCorp or Quest laboratories
 - Organ procurement and transplant network (OPTN)
 - Social Security Death Index (SSDI)/Obituary search
- PBC defined by diagnosis code, high ALP, UDCA treatment history, and no competing diagnosis.
- Pharmacy claims to define OCA exposure
- Diagnosis coded on hospital claims to identify hepatic decompensation outcomes
- OPTN to identify date for liver transplantation
- SSDI/Obituary search to identify date of death



Applicant's Proposed Indication and Dosage

- Applicant's Revised Proposed Indication:
 - To reduce the risk of death, liver transplant, and hepatic decompensation in adults with 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
- Proposed Dosage Regimen
 - 5 mg titrated to 10 mg, orally once daily

Discussion Questions for the AC

1. Discuss whether the evidence generated post-approval verify the benefit of obeticholic acid (OCA, Ocaliva®) on clinical outcomes (hepatic decompensation, liver transplant, and death) in adults with PBC? Specifically, discuss the evidence generated in the:
 1. Post-marketing required Study 302, and
 2. Observational Study 405
2. Discuss the safety of OCA, including the incidence of liver transplant and all-cause death in the United States Prescribing Information (USPI)-labeled and the overall study population.



Voting Questions for the AC

1. Does the available evidence verify the benefit of OCA on clinical outcomes (hepatic decompensation, liver transplant, and death) in the USPI-labeled population? Provide a rationale for your vote.
2. Is the benefit-risk profile of OCA favorable in the USPI-labeled population? Provide a rationale for your vote.

Clinical Pharmacology

Tao Liu, PhD (Presenter)

Insook Kim, PhD

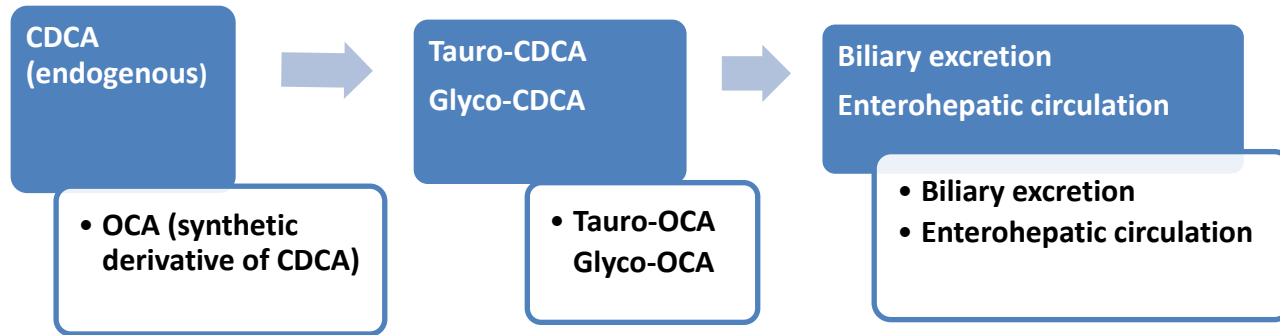
Division of Inflammation and Immune Pharmacology (DIIP)

Office of Clinical Pharmacology (OCP)

OTS, CDER, FDA

OCA is a Synthetic Bile Acid

- Synthetic derivative of chenodeoxycholic acid (CDCA)
- For elimination, OCA shares similar pathways with endogenous bile acids

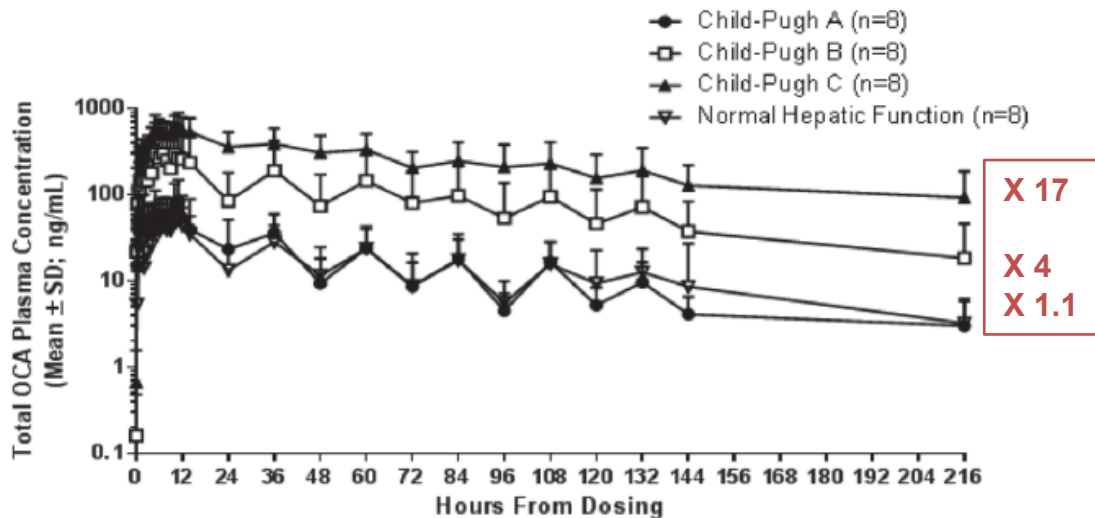


- Major active conjugates with substantially higher exposure than OCA
 - Long half-life
 - Substantial exposure accumulation following multiple doses
 - Systemic exposure presented as total OCA concentration (= OCA + Tauro-OCA + Glyco-OCA)
- **Liver dysfunction significantly affects the pharmacokinetics (PK) of OCA and its major conjugates**

Significant and Variable Impact of Hepatic Impairment (HI) on PK

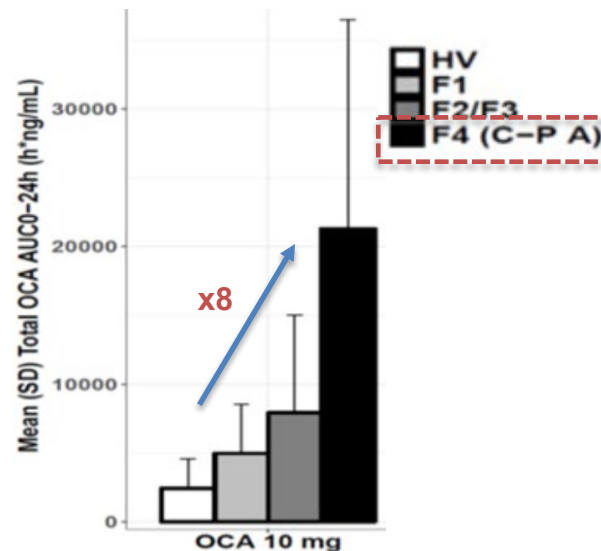


Total OCA Concentrations Versus Time After Single-Dose Administration¹



⇒ Same Dose for Noncirrhotic and CP-A
 ⇒ Dose Reduction for CP-B and CP-C

Total OCA Exposure at Steady-State²



PK variability within CP-A class

¹Clinical Pharmacology Review of Original NDA 207999 (2016)

²FDA GIDAC Briefing Document for NDA 212833 (2023)

Evolution of Dosing Regimen in Study 302

- Protocol in 2015
 - All patients start at 5 mg once daily (QD) regardless of HI
 - In 2016, FDA approved the reduced dosage for subjects with moderate to severe HI¹
 - Dosing Regimens in Protocol Version 3 (Sept. 2017)
 - Patients without cirrhosis or with mild HI (CP-A)
 - 5 mg QD => 10 mg QD
 - Patients with moderate to severe HI (CP-B and CP-C)
 - 5 mg once weekly => 5 mg twice weekly => 10 mg twice weekly if tolerated
 - Dosage adjustment based on biochemical response and tolerability
- => Resulted in variable daily dose by cirrhosis status and over time**

Planned and Studied Dosing Regimens in Study 302

Number of Subjects in OCA Arm per Baseline Cirrhosis Status and USPI Status¹

Cirrhosis Status at Baseline	USPI Status	Dosage Regimen ² (Starting Dose/Maximum Dose)	
		5 mg QD/10 mg QD	5 mg QW/10mg BIW
No cirrhosis	Labeled	78	
Compensated	Labeled	3 (CP-A)	
	Contraindicated	55 (CP-A with CSPH*)	
Decompensated	Contraindicated	8 (CP-A with CSPH*)	5 (CP-B) 19 (CP-B with CSPH*)

QD: once daily
 QW: once a week
 BIW: twice a week
 QOD: once every other day

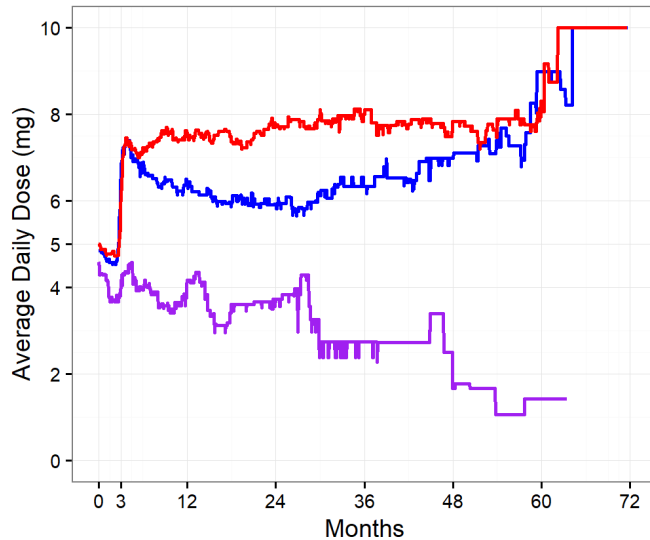
* CSPH: clinically significant portal hypertension

Dosage Adjustment In USPI Labeled Population

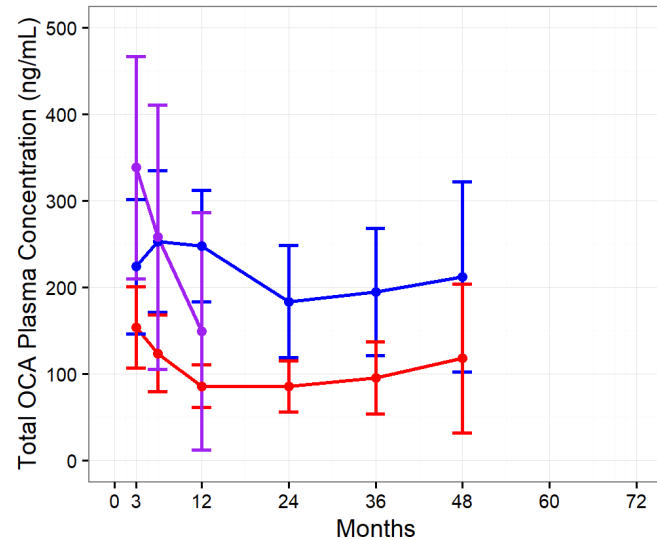
- 54 out of 81 subjects were up titrated to 10 mg QD as planned
 - 21 out of 54 subjects (39%) were down titrated from 10 mg QD
 - 11 subjects (22%) were down titrated from 10 mg due to pruritus and other AEs

Lower Daily Dose and Higher Total OCA C_{trough} in PBC Subjects With Cirrhosis Versus Without Cirrhosis

Average Daily Dose



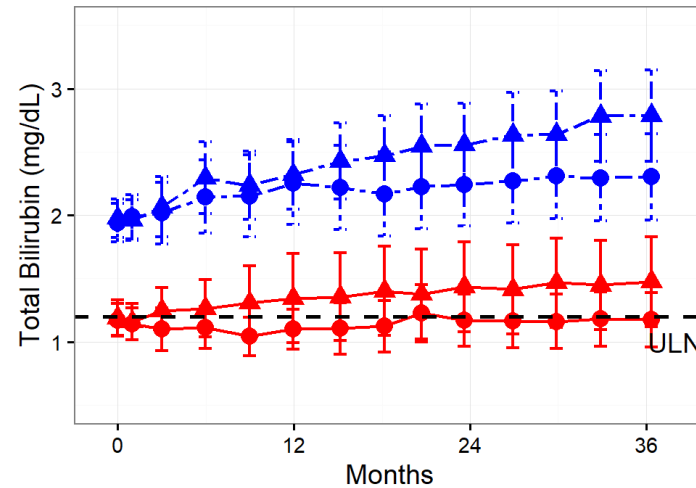
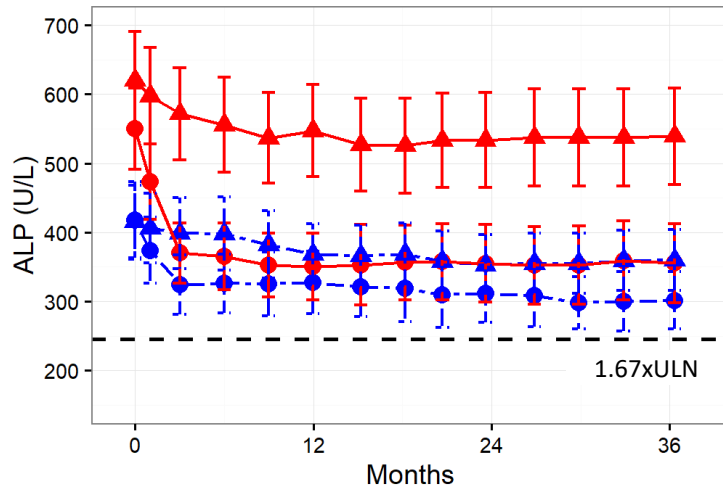
Mean Trough Concentration



- Compensated cirrhosis
- Non-cirrhotic
- Decompensated cirrhosis

Study 302

Mean ALP Decreased but Remained > 1.67xULN in OCA Treated USPI Labeled Population



Number of subjects

Placebo	68	49	30	20
OCA	81	59	46	31

Placebo	68	49	29	20
OCA	81	59	45	31

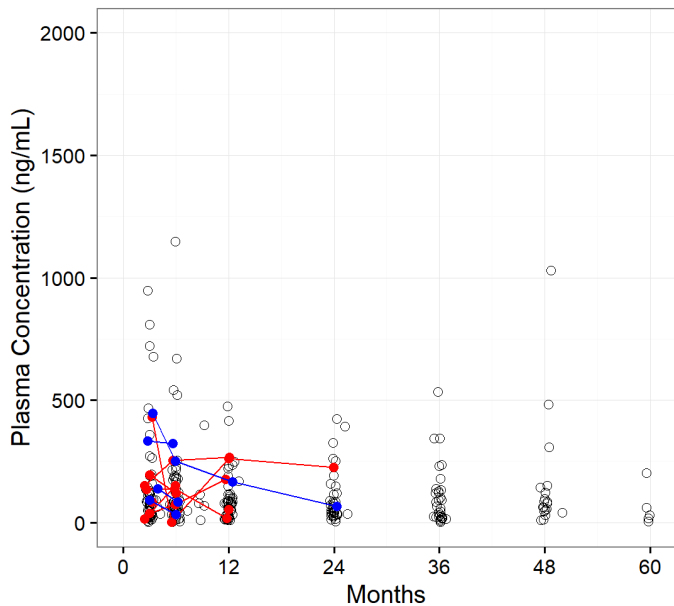
Placebo	98	73	41	22
OCA	87	57	40	30

Placebo	98	73	41	22
OCA	87	57	40	30

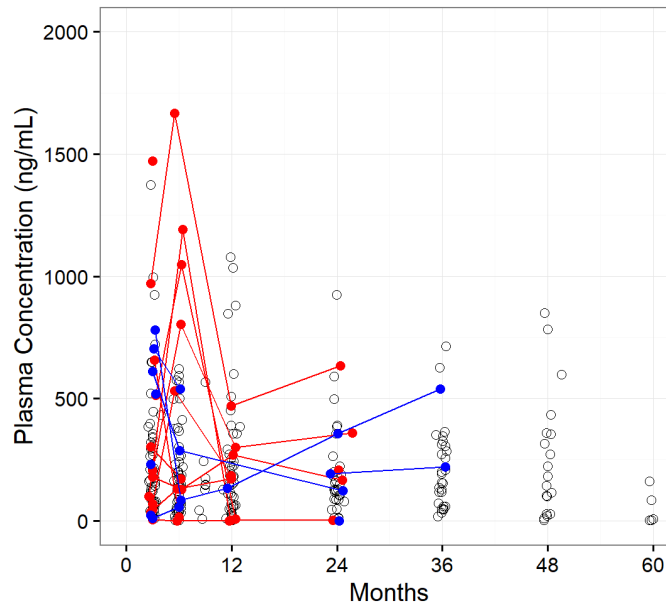
	OCA USPI-contraindicated		OCA USPI-labeled
	Placebo USPI-contraindicated		Placebo USPI-labeled

Comparable Total OCA C_{trough} Between USPI Labeled Population With or Without Liver Transplantation or Death

USPI Labeled



USPI Contraindicated



Red circle: subjects who underwent liver transplantation (LT)

Blue circle: subjects died

Black open circle: subjects without LT or death

Summary of Clinical Pharmacology Findings in USPI Labeled Population of Study 302

- Mean total OCA concentration was similar to historical data in PBC subjects
- Mean ALP was decreased within four months and was lower in OCA subjects compared to placebo subjects but remained $> 1.67 \times \text{ULN}$ in both cohorts
- At month 12, the biochemical response¹ rate was 14% in OCA and 3% in placebo
- In USPI-labeled population, events of liver transplantation or death were not associated with higher total OCA concentrations

STUDY 747-302

Tram Tran, MD FACG FAASLD (Presenter)
Division of Hepatology and Nutrition (DHN)
Office of Inflammation and Immunology (OII)
Office of New Drugs (OND)
CDER, FDA

Yura Kim, PhD CDER/OTS/OB/DBIII
Rebecca Hager, PhD CDER/OTS/OB/DBIII
Ping Li, MS CDER/OTS/OB/DAI

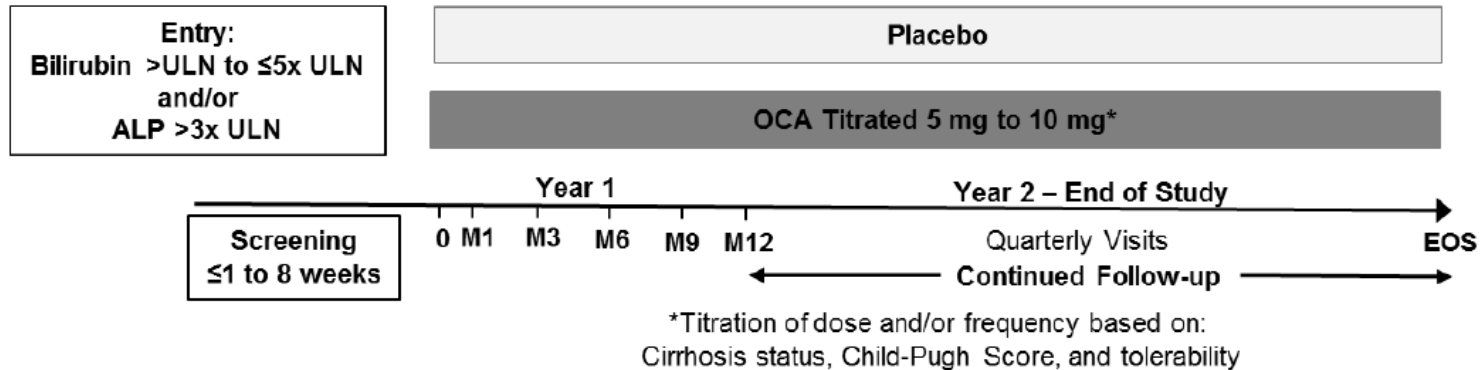
STUDY 747-302



- Study Design
- Interpretability
- Efficacy Analysis
- Safety Analysis
- Benefit-Risk Assessment

Study 747-302: Design

- Randomized, double-blind, placebo-controlled trial conducted from December 2014 to December 2021
- A total of 334 adult subjects with PBC were randomized in a 1:1 ratio to OCA or placebo
- Event-driven trial with final analysis planned to occur after accrual of 127 primary endpoint events



Source: Applicant Protocol Version 6 for Trial 747-302, pg. 31. EOS = end of study; ULN = upper limit of normal

Applicant's Criteria for USPI-Contraindicated Population



Key Clinical Severity Criteria	
Clinically Significant Portal Hypertension (CSPH)	Decompensated Liver Disease
Transjugular intrahepatic portosystemic shunt (TIPS), variceal sclerotherapy or ligation	Child-Pugh (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 x 10 ⁹ /L with splenomegaly and/or with transient elastography >15 kPa	

The **USPI-labeled subgroup** included intent-to-treat (ITT) subjects who **did not have any history or evidence of** clinically significant portal hypertension (CSPH) or decompensation at baseline

Source: Clinical reviewer modified from Applicant CSR Table 16 page 87 HTN: hypertension, SBP: spontaneous bacterial peritonitis, USPI: United States Package Insert

Baseline Characteristics

Characteristic	ITT Population (%)	USPI-Labeled (%)
USPI status		
Contraindicated	55%	
Labeled	45%	100%
Disease Stage		
Non-cirrhotic	42%	94%
Compensated Cirrhosis	37%	6%
Decompensated Cirrhosis	21%	-
Rotterdam Criteria		
Early	32%	57%
Moderate	62%	42%
Advanced	7%	1%

Source: Reviewer modified from Applicant CSR Table 26 page 115 ITT: Intent-to-Treat, USPI: United States Package Insert

Study 747-302: Interpretability

- FDA finds that Trial 747-302 provides meaningful and interpretable data to inform the benefit-risk of OCA
- Large, randomized, placebo-controlled trial for a rare disease
- Power was adequate in ITT population under prespecified assumptions
- Randomized arms were similar in terms of
 - On-study follow up time and study withdrawal rates
 - Concomitant medication use
- The study evaluates the treatment effect under real world levels of treatment adherence to OCA
- Observed trends of efficacy are largely driven by biomarkers
- Outcomes of transplant and death are least likely to be affected by potential recall bias or differences in frequency of data collection

Study 747-302: Interpretability

- Crossover to commercial OCA (cOCA) was imbalanced
 - 16% in placebo arm vs. 8% in OCA arm in ITT population
 - 12% in placebo arm vs. 5% in OCA arm in USPI-labeled population
- Crossover makes it potentially more difficult to identify differences between randomized treatment arms
 - The observed magnitude of efficacy and safety signals may be smaller than without crossover.
 - Safety signals of OCA on liver transplant/death could be underestimated due to placebo crossover to cOCA



STUDY 747-302: EFFICACY

Analysis Populations

- Intent-to-Treat (ITT) and Safety populations include all N=334 randomized subjects
 - 45% of subjects (N=149) are in the **USPI-labeled population**
 - 55% of subjects (N=185) are in the **USPI-contraindicated population**
- Prespecified that efficacy analyses be conducted in the ITT population
- Efficacy also evaluated in the USPI-labeled population

Power and Primary Endpoint Expansion

- Power calculations required **at least 127 events** to achieve 80% power with an assumed hazard ratio of 0.6, the effect size assumed by the Applicant.
- In December 2021, the definition of the primary endpoint was expanded to increase the number of clinical outcome events.
- In the ITT population:
 - **151 events** were observed on the expanded primary endpoint
 - **96 events** were observed on previously-defined primary endpoint
- With the expanded primary endpoint, the 151 events exceeded the 127 events required to achieve 80% power in the ITT population under the assumed effect size

Expanded Primary Endpoint – Time to First Event



<p><i>All subjects (events are denoted “Group 1 events”)</i></p> <ul style="list-style-type: none">• Death (all-cause)• Liver transplant• Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:<ul style="list-style-type: none">○ Variceal bleed○ Hepatic encephalopathy (as defined by a West Haven score of ≥ 2)○ Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis OR presence of $>250/\text{mm}^3$ polymorph leukocyte [PMNs] in the ascitic fluid)○ Bacterial empyema (confirmed by diagnostic thoracentesis OR presence of $>250/\text{mm}^3$ PMNs in the pleural fluid)• Uncontrolled or refractory ascites (requiring large volume paracentesis)• Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club , portopulmonary syndrome, or hepatopulmonary syndrome)• MELD-Na score ≥ 15 (for subjects with baseline MELD-Na score < 12)• MELD score ≥ 15 (for subjects with baseline MELD-Na score ≥ 12)
<p><i>Subgroup of subjects without decompensation at baseline</i></p> <ul style="list-style-type: none">• 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
<p><i>Subgroup of subjects without decompensation or clinical evidence of portal hypertension at baseline</i></p> <ul style="list-style-type: none">• 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 $< 150 \times 10^9/\text{L}$ with splenomegaly and/or with transient elastography > 15 kPa

Primary Endpoint (Group 1 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 $>250/\text{mm}^3$ polymorph leukocyte [PMNs] in the ascitic fluid)**
 - **Bacterial empyema (confirmed by diagnostic thoracentesis OR presence of $>250/\text{mm}^3$ PMNs in the pleural fluid)**
- **Uncontrolled or refractory ascites (requiring large volume paracentesis)**
- Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club , portopulmonary syndrome, or hepatopulmonary syndrome)
- MELD-Na score ≥ 15 (for subjects with baseline MELD-Na score < 12)
- **MELD score ≥ 15 (for subjects with baseline MELD-Na score ≥ 12)**

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

Source: FDA Briefing Document Table 3 Modified from Applicant CSR Table 2 page 31

Primary Endpoint (Other Events)

<p><i>Subgroup of subjects without decompensation at baseline</i></p> <ul style="list-style-type: none"> • 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
<p><i>Subgroup of subjects without decompensation or clinical evidence of portal hypertension at baseline</i></p> <ul style="list-style-type: none"> • 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 $< 150 \times 10^9/L$ with splenomegaly and/or with transient elastography > 15 kPa

Source: FDA Briefing Document Table 3 Modified from Applicant CSR Table 2 page 31



Key Secondary Endpoints

1. Time to first occurrence of any Group 1 events
2. Time to first occurrence of events in **bold** on previous slides (primary endpoint prior to expansion)
3. Time to liver transplant or all-cause death

Treatment and Study Discontinuation

- Most common reason for treatment discontinuation was an adverse event (AE).
 - 39% in OCA group and 31% in placebo group
- Follow up was planned for subjects who discontinued study drug, either with study visits, phone calls, or review of electronic medical records
- On-study follow-up time was similar across the two arms in the USPI-Labeled, USPI-Contraindicated, and ITT populations

Commercial OCA and Concomitant Medication



Table: Use of Commercial OCA and Concomitant Medication, ITT Population

Medication	OCA N=168			Placebo N=166		
	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

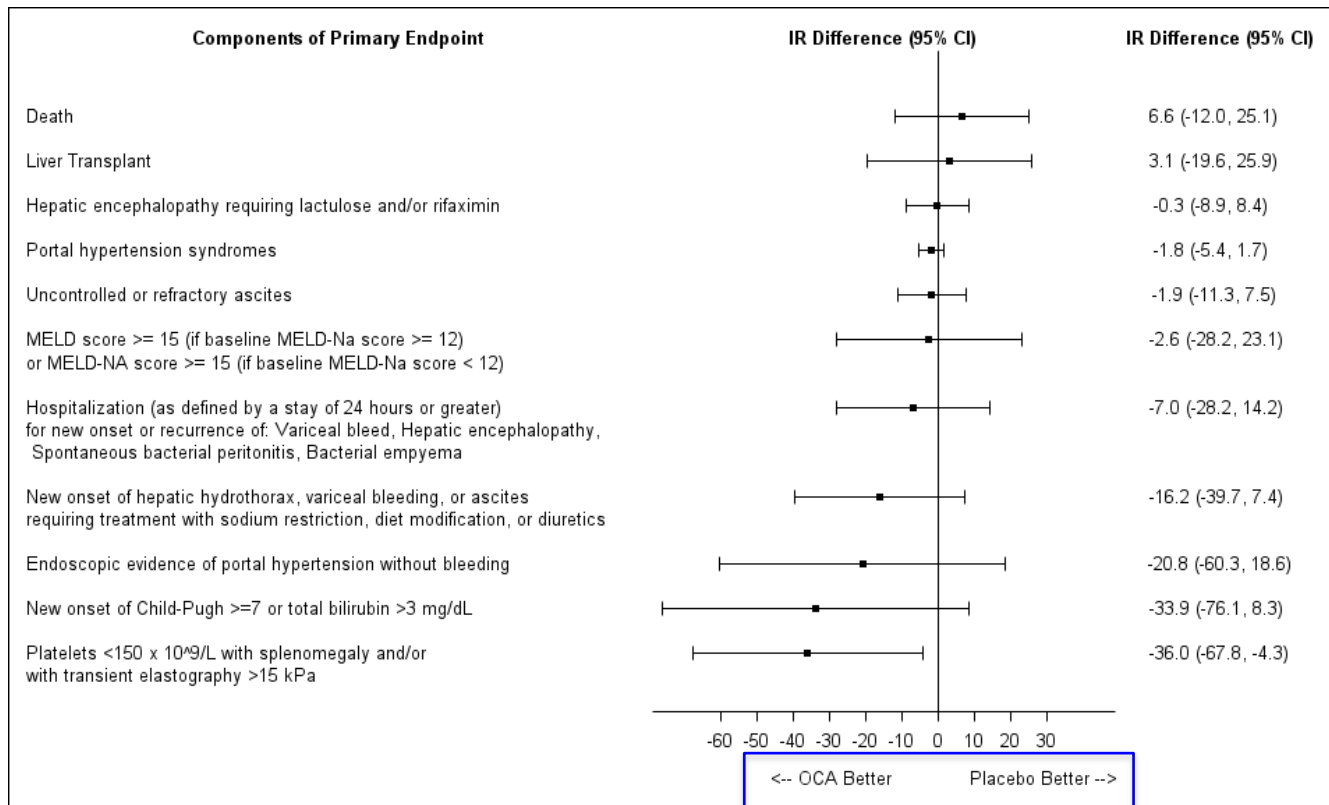
Abbreviations: OCA, Obeticholic Acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic UDCA, ursodeoxycholic acid

- More commercial OCA use in the placebo arm (16%) compared to the OCA arm (8%)
- Use of other concomitant medications was similar across the two arms
- Similar trends in the USPI-labeled population

Primary Endpoint Results

- ITT population results were not statistically significant (prespecified primary analysis)
 - **Hazard ratio (HR) = 0.84 (95% confidence interval [CI]: 0.61, 1.16), p-value = 0.304**
- USPI-labeled population had a point estimate of the hazard ratio that was consistent with the ITT population results
 - HR = 0.88 (95% CI: 0.47, 1.65)

Incidence Rate Differences for Components of the Primary Endpoint (ITT Population)

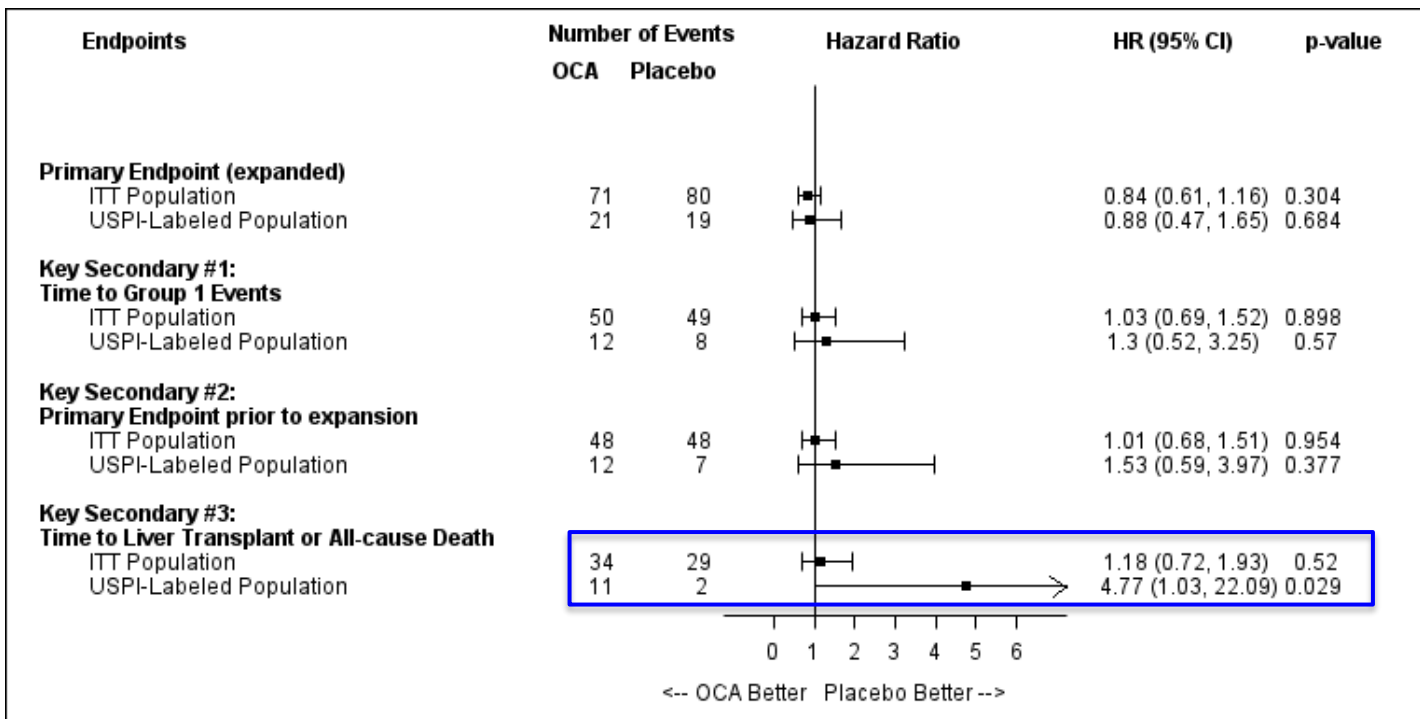


Source: Statistical reviewer analysis using Applicant submitted dataset adevt,xpt and adsl.xpt

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)

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

Primary and Key Secondary Endpoint Results



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

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. The p-value is from the log rank test stratified by the randomization stratification factors.

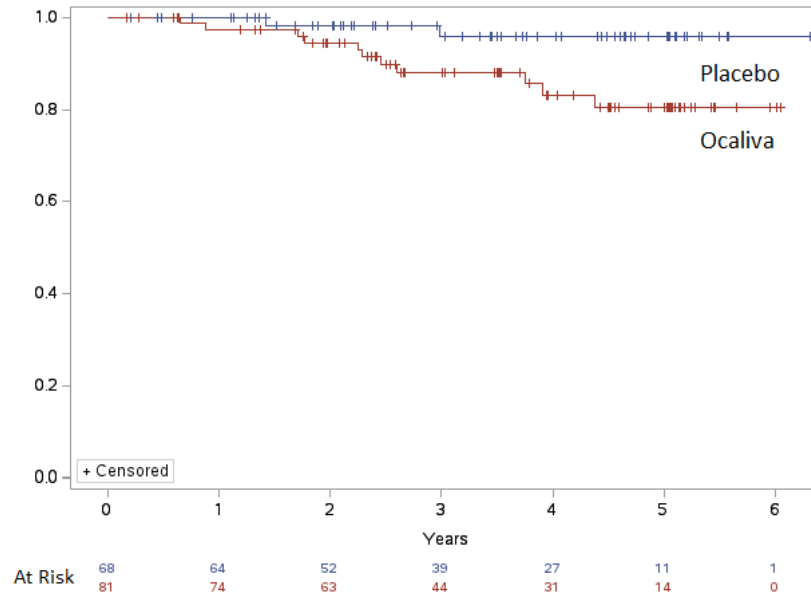
Abbreviations: OCA, Obeticholic Acid; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval

Transplant-Free Survival (USPI-Labeled Population)



- Trend of harm of OCA compared to placebo on transplant-free survival
- HR = 4.77 (95% CI: 1.03, 22.09)
- 11 vs. 2 death/liver transplant events in the OCA vs. placebo arms

Figure: Probability of Transplant-Free Survival, USPI-Labeled Population



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



STUDY 747-302: SAFETY

Study 747-302: Liver Transplant Recipients



Liver Transplant	OCA	Placebo
Total Safety/ITT Population	20	18
Commercial OCA or PK test positive for OCA		7
USPI- Contraindicated	13	17
Commercial OCA or PK test positive for OCA		6
USPI- Labeled	7	1
Commercial OCA exposure		1

- Eight subjects in the USPI-labeled population required liver transplant:
 - 7 were in the OCA treatment arm and 1 in the placebo arm
 - The placebo-treated subject received placebo for 268 days; on Day 269 switched to commercial OCA and received OCA for ~2 years prior to liver transplant.

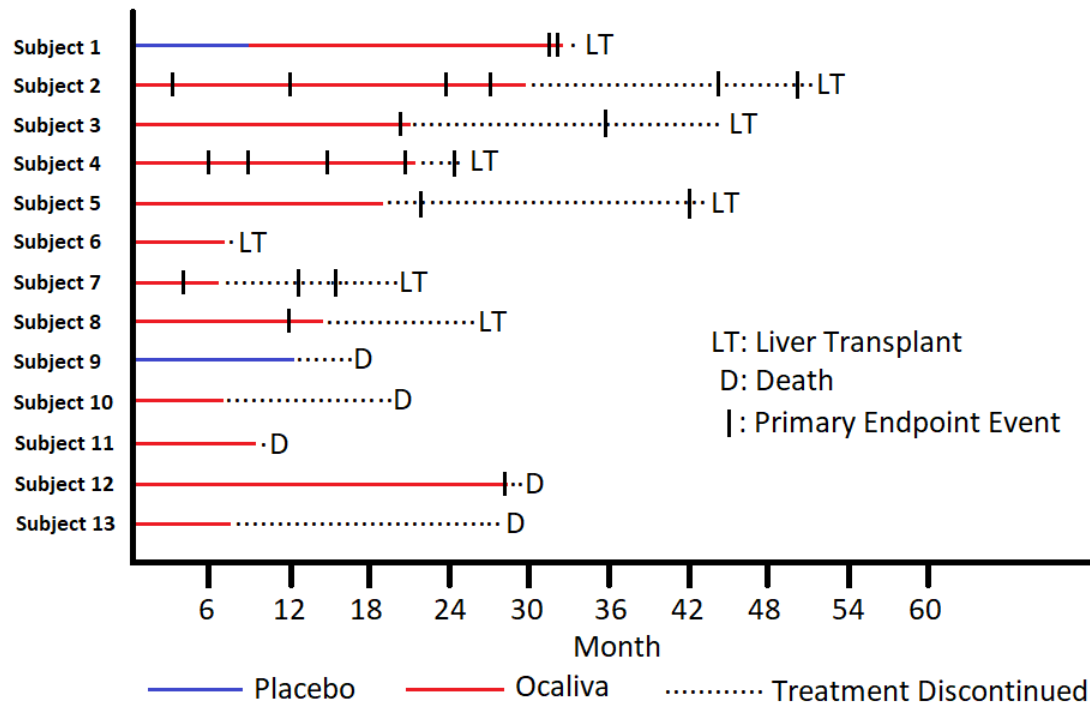
Study 747-302: All Liver Transplants; USPI-Labeled Population



Subject	Age /Sex	Treatment Arm	Cirrhosis Status at Baseline	Last Day IP /OLT Study Day	Review Findings
Sub 1	47/F	Placebo*	Noncirrhotic	268/1078 Commercial OCA: Days 269-985/1078	Multiple portal hypertensive bleeds, ascites.
Sub 2	49/M	OCA	Noncirrhotic	912/1580	Subject with progressive increase in TB on IP ; episodes of recurrent anemia, portal hypertensive bleed
Sub 3	40/F	OCA	Noncirrhotic	611/1412	Subject with increase in TB 1.8 baseline to 4.1, CP 5A to 8B on IP; MELD eventually to 23
Sub 4	43/F	OCA	Cirrhotic	667/812	Subject with increasing TB and MELD score on IP
Sub 5	44/F	OCA	Noncirrhotic	593/1356	Subject with worsened pruritus on IP, biopsy: noncirrhotic PBC. Progressive jaundice post DC of study drug
Sub 6	58/F	OCA	Noncirrhotic	221/234	Subject with pruritus indication for OLT; TB 0.6 mg/dL, MELD 6.4. Explant with stage 2 fibrosis, ductopenia
Sub 7	43/F	OCA	Cirrhotic	199/639	Subject with increased transaminases and CP score on IP (5A to 7B), progression to OLT off IP.
Sub 8	43/F	OCA	Noncirrhotic	434/823	Subject with progressive jaundice , recurrent pruritus and OLT

Source: generated by clinical reviewer from Applicant CSR *received placebo for 268 days and switched to commercial OCA on day 269

Study 747-302: Clinical Trajectory Liver Transplant and Death in USPI-Labeled Population





STUDY 747-302: ALL-CAUSE DEATH

Study 747-302: All-Cause Death

Population	OCA	Placebo
Deaths Overall Safety/ITT Population	16	12
OCA Positive PK Samples or Documented cOCA		3
Deaths in the Contraindicated Population	12	11
OCA Positive PK Samples or Documented cOCA		3
Deaths USPI-Labeled Population	4	1

- Total deaths =28
- USPI-labeled population deaths, n=5
 - OCA=4
 - Portal hypertension/GIB complications
 - Multiorgan failure
 - Subdural hematoma
 - Lymphoma
 - Placebo=1
 - Cardiac arrest

Subject Case Review – Liver-Related Death



Study Day	Day (-1)	Start OCA	Day 378	Day 532	Day 665	Day 819	Day 899: OCA DC	Day 937 Death
ALT (U/L)	155		88	130	168	91		
TB (mg/dL)	2.0		0.6	0.3	5.0	0.8		
INR	0.9		1.0	0.9	1.0	0.9		
ALB (g/dL)	4.1		3.9	3.6	4.0	4.1		
ALP (U/L)	453		313	359	715	258		
MELD	9.1		6.4	6.4	12.5	6.4		
Platelets	224					173		
		Study day 3 EGD: No evidence of varices Positive for esophagitis chronic gastropathy hiatal hernia	EGD : Large EV Hypertensive gastropathy HOC Committee: “Progression to cirrhosis” HOC committee		UTI: drug holiday		Hospitalization for GIB	Death: Multiple UGIB, shock, cerebral edema. HOC Committee: “Liver-related” death

Source: Applicant HSAC narrative

Abbreviations: DC- discontinuation; EGD-esophagogastroduodenoscopy, EV esophageal varices, HOC-Hepatic Outcomes Committee, UTI-urinary tract infection, UGIB-upper gastrointestinal bleed
MELD-Model Endstage Liver Disease, PLT-platelets, ALP-alkaline phosphatase ALB-albumin, TB-total bilirubin, ALT-alanine aminotransferase INR-international normalized ratio, Platelet units: 10⁹/L



STUDY 747-302: DRUG-INDUCED LIVER INJURY (DILI)

Study 747-302: DILI Assessments

Overall, Contraindicated, USPI-Labeled Populations



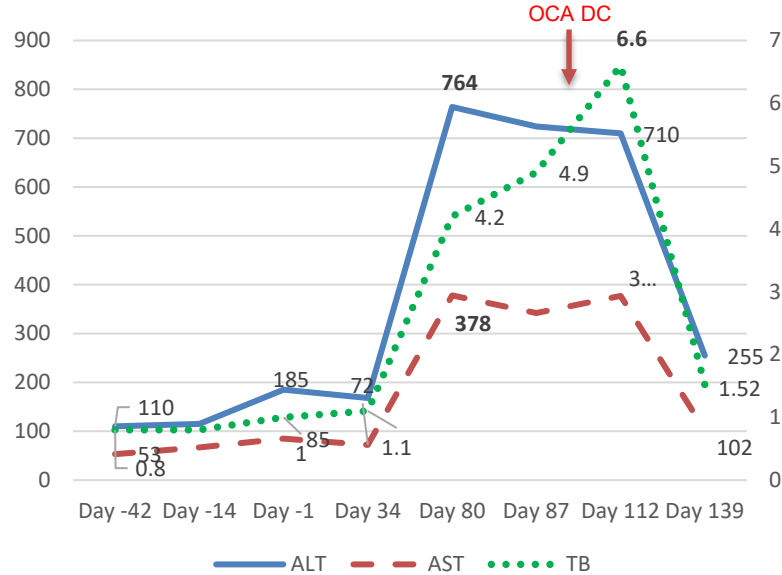
HSAC DILI Adjudication	OCA	Placebo
	Overall Safety Population n=168	Overall Safety Population n=166
Probable DILI	1 (0.59%)	0 (0%)
Possible DILI	17 (10%)	8 (4.8%)
TOTAL	18 (10.7%)	8 (4.8%)
	USPI-Contraindicated n=87	USPI-Contraindicated n=98
Probable DILI	1 (1.1%)	0 (0%)
Possible DILI	13 (14.9%)	7 (7.1%)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

Source: Trial 747-302 Applicant Hepatic Safety Adjudication Committee Primary Endpoint Relatedness Adjudication Package pages 2-47

DILI Case Review

- **45-year-old woman on OCA, USPI-labeled population**
- **PMH:**
 - PBC diagnosed by liver histology in 2013. Subject experienced fatigue, pruritus, hypertension (HTN), arthritis, Sjogren’s Syndrome, hypercholesterolemia, and constipation.
 - Liver biopsy, 2016: no evidence of autoimmune hepatitis (AIH).
- **Meds:**
 - Oral contraceptive (OCP), hydroxyzine, ibuprofen (arthritis), prednisone 5 mg (arthritis) – omeprazole, simvastatin, lactulose (constipation), *cholestyramine, colesevelam (pruritus)*

DILI Case Review-Trends in Liver Chemistry



**HSAC Blinded
Adjudication 2/2023:**
Possible DILI
Probable DILI
Probable DILI

**HSAC Blinded
Adjudication 4/2023:**
Possible DILI
Possible DILI
Highly Likely DILI

Study Day	Day -14	Day -1	Day 34	Day 57	Day 80	Day 87: (OCA DC'd)	Day 112	Day 139
ALT (U/L)	115	185	168		764	724	710	255
AST (U/L)	67	85	72		378	342	377	102
ALP (U/L)	527	574	440		460	479	446	688
TB (mg/dL)	0.8	1	1.1	1.58	4.2	4.9	6.6	1.52



STUDY 747-302: PRURITUS

Study 747-302: Pruritus



USPI-Labeled Population	OCA N=81 n/PY (IR)	Placebo N=68 n/PY (IR)	IR Difference (95% CI)
Pruritus TEAE on study	67/65.2 (102.7)	36/92 (39.0)	63.7 (37.5,93.6)
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: Applicant Table R24.3 Aug 6 2024, IR page 12; CDS adae.xpt; Software: R PY- person-years IR- incidence rate CI- confidence interval
TEAE- treatment-emergent adverse event SAE- serious adverse event

Safety Summary

- In the overall ITT/Safety population, OCA treated subjects had higher numbers of clinical events of liver transplant and death compared to the placebo group.
 - This difference may be underestimated due to placebo crossover with commercial OCA.
 - Notable also in the USPI-labeled subpopulation
- The overall, contraindicated, and USPI-labeled population had higher events of possible or probable DILI.
- Higher incidence differences for pruritus for OCA treatment

Benefit-Risk Assessment



The Agency asserts that Study 747-302 provides interpretable and informative results regarding the benefit-risk for OCA.

Benefit

- Biochemical response at month 12 (OCA 10% vs. placebo 2%)
- Randomized, controlled clinical trial failed to demonstrate efficacy on the primary endpoint (hazard ratio of 0.84 [95% CI: 0.61, 1.16] ($p=0.304$) for the ITT population)

Risks

- Signal of harm on liver transplant/death
 - ITT population : hazard ratio of 1.18 [95% CI: 0.72, 1.93]
 - USPI-labeled population: 4.77 [95% CI: 1.03, 22.09]
- Higher risk of DILI and pruritus as adverse events
- Concerns for feasibility of risk mitigation due to unpredictable nature of hepatotoxicity observed in USPI-labeled population



Study 747-405

Joel L. Weissfeld, MD, MPH

Senior Medical Officer

Division of Epidemiology (DEPI)

Office of Pharmacovigilance and Epidemiology (OPE)

Office of Surveillance and Epidemiology (OSE), CDER, FDA



**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](#))**

STUDY 747-405: OUTLINE

- **Study design, data sources, and methods**
- Key study results
- Data relevance and reliability

STUDY 747-405: Study Design (1)

- 67-month (June 2016 – December 2021) observational (non-randomized) cohort study conducted in a U.S. health insurance database
- Target Trial Emulation
 - articulate causal question in the form of an imaginary protocol for a hypothetical randomized trial, i.e., OCA trial design to assess clinical outcomes in the USPI-labeled PBC population
 - emulate components of the imaginary protocol with observational data

STUDY 747-405: Study Design (2)

- Treatment Decision Design—Each occurrence of observed abnormality in ALP (>121 U/L) or bilirubin (BILI) (>1.2 mg/dL) conceived as a decision point whereby a healthcare provider might prescribe or not prescribe OCA
- Implications
 - Defined an untreated control
 - Allowed more than one follow-up period from the same patient



STUDY 747-405: Data Sources

- Administrative claims against health insurance (KOMODO)
- Used DATAVANT to link claims to
 - Laboratory tests (LabCorp and Quest Diagnostics)
 - Date of liver transplantation (Organ Procurement and Transplantation Network)
 - Date of death (Social Security Death Index and Obituary Search)

STUDY 747-405: Methods (1)

- Inclusion Criteria
 - Age ≥ 18 years
 - Definite or probable PBC (≥ 1 inpatient claim or ≥ 2 outpatient claims on different dates)
 - UDCA-treatment failure
 - ALP > 121 U/L or BILI > 1.2 mg/dL
 - Closed claims available for ≥ 12 months before an index date used to start a period of follow-up

STUDY 747-405: Methods (2)

- UDCA Treatment Failure
 - Inadequate Response – ALP or BILI above upper limit of normal (ULN) despite ≥ 270 days of UDCA in previous 365 days and ≥ 60 days of UDCA in previous 90 days
 - Intolerance – high ALP or BILI observed >90 days after a single episode of UDCA treatment lasting ≤ 90 days
 - Discontinued – (a) high ALP or BILI recorded ≥ 6 months after completing most recent UDCA course; or (b) any UDCA before initiating treatment with OCA

STUDY 747-405: Methods (3)

- Exclusion Criteria
 - Concomitant liver disease (hepatitis C, hepatitis B, alcoholic liver disease, or primary sclerosing cholangitis)
 - History of hepatic decompensation (variceal bleed, ascites, spontaneous bacterial peritonitis, hepatic hydrothorax, or hepatic encephalopathy)
 - Laboratory test indicators for hepatic decompensation or hepatobiliary injury (BILI >3 mg/dL, ALP >10 × ULN, ALT >10 × ULN, AST >10 × ULN)

STUDY 747-405: Methods (4)

- Exposure – Sequence of OCA dispensings (as indicated by pharmacy claims against health insurance) with 90-day treatment gaps allowed between dispensings and 90 days added to a last dispensing

STUDY 747-405: Methods (5)



- Study Outcomes
 - Hepatic Decompensation Event – hospital claim with diagnosis coding for variceal bleeding, ascites, or hepatic encephalopathy
 - Liver Transplantation – link to OPTN Registry or consistent claims profile
 - Death – link to SSDI or Obituary Search

STUDY 747-405: Methods (6)



Hepatic Decompensation (ICD-10)

Variceal Bleeding

I85.01 Esophageal varices with bleeding
I85.11 Secondary esophageal varices with bleeding

Ascites

K70.11 Alcoholic hepatitis with ascites
K70.31 Alcoholic cirrhosis of liver with ascites
K71.51 Toxic liver disease with chronic active hepatitis with ascites
R18.0 Malignant ascites
R18.8 Other ascites
J94.8 Other specified pleural condition – applicable to hydrothorax
K65.2 Spontaneous bacterial peritonitis

Hepatic Encephalopathy

G93.40 Encephalopathy, unspecified
B15.0 Hepatitis A with hepatic coma
B16.0 Acute hepatitis B with delta-agent with hepatic coma
B16.2 Acute hepatitis B without delta-agent with hepatic coma
B17.11 Acute hepatitis C with hepatic coma
B19.0 Unspecified viral hepatitis with hepatic coma
B19.11 Unspecified viral hepatitis with hepatic coma
B19.21 Unspecified viral hepatitis C with hepatic coma
K70.41 Alcoholic hepatic failure with coma
K72.01 Acute and subacute hepatic failure with coma
K72.11 Chronic hepatic failure with coma
K72.90 Hepatic failure, unspecified without coma
K72.91 Hepatic failure, unspecified with coma

STUDY 747-405: Methods (7)



Covariates Included in Propensity Score Model

Fixed

Sex (female, male)

Assessed over $[-\infty, 0]$ -day pre-index period

Cirrhosis

Clinical evidence of portal hypertension

Charlson Comorbidity Index (discrete integer score)

Updated on index date

Calendar period (2016-2020, 2020-2021)

Age (discrete integer year)

Health insurance type (six categories)

Months since UDCA failure (continuous)

On UDCA (yes, no)

Most recent value in $[-365, 0]$ -day pre-index period

Alkaline phosphatase (ALP)

Total bilirubin (BILI)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Platelet count

STUDY 747-405: Methods (8)



- Follow-Up and Analysis
 - As-treated time to death, liver transplantation, or hepatic decompensation

STUDY 747-405: OUTLINE

- Study design, data sources, and methods
- **Key study results**
- Data relevance and reliability

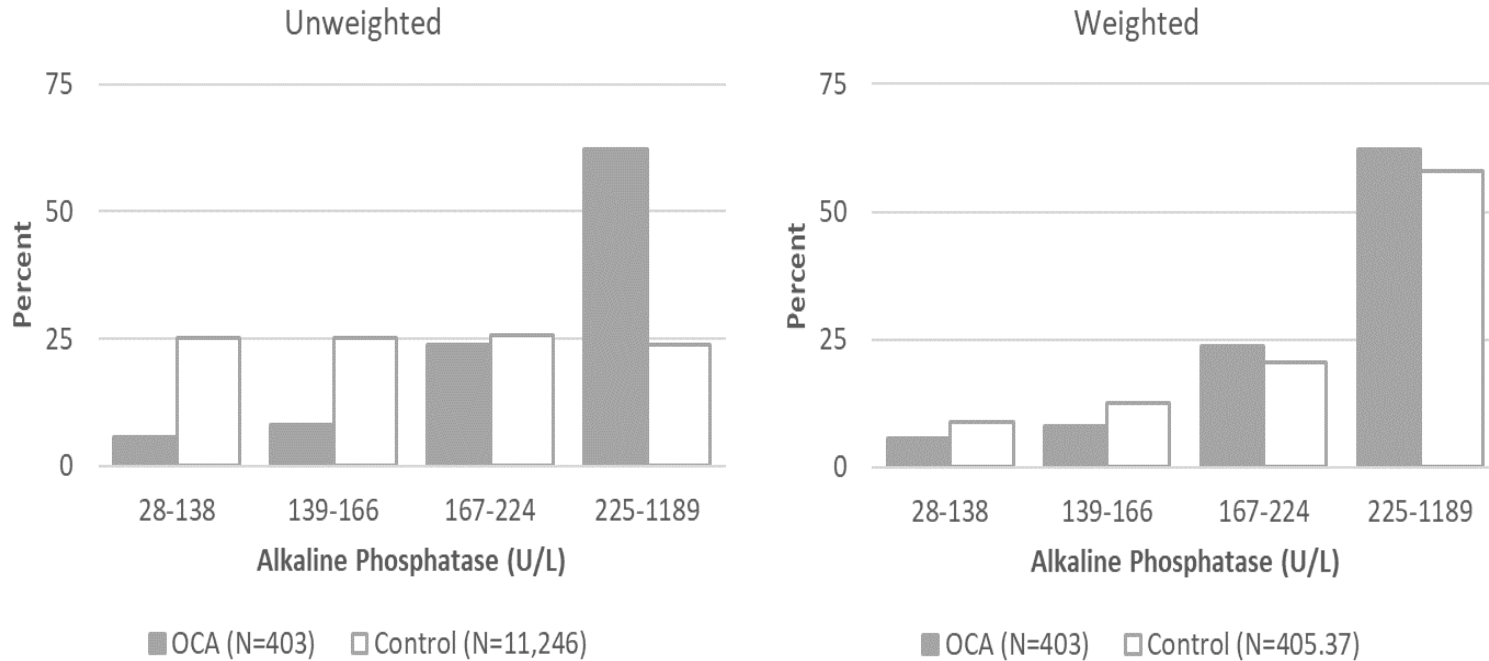
STUDY 747-405: Key Study Result (1)

Baseline Characteristics

Parameter	Treated With OCA N=403	Not Treated With OCA Unweighted N=11,246	Not Treated With OCA Weighted N=405.37
Sex, female, n (%)	369 (91.6)	10,146 (90.2)	369.47 (91.1)
Age, years, mean (SD)	56.2 (10.6)	61.1 (11.7)	55.9 (12.6)
Cirrhosis, n (%)	203 (50.4)	4,936 (43.9)	204.57 (50.5)
Portal hypertension, n (%)	95 (23.6)	2,887 (25.7)	94.97 (23.4)
On UDCA, n (%)	292 (72.5)	7,236 (64.3)	294.57 (72.7)
ALP, U/L, mean (SD)	292 (154)	199 (104)	294 (153)

SOURCE: CSR Tables 14.1.15, 14.1.16, 14.1.18, 14.1.20, 14.1.23, and 14.1.24

STUDY 747-405: Key Study Result (2)



SOURCE: Reviewer analysis of ADaM dataset (ADID)



STUDY 747-405: Key Study Result (3)

Applicant's Primary Analysis

Parameter	Treated With OCA	Not Treated with OCA
	N=403	N=405.37 (WEIGHTED)
As-treated follow-up		
Mean (days)	436	627
Maximum (months)	63	67
Treatment switch, n (%)	215 (53.3)	85.37 (21.1)
DTH/LT/HD		
n (%)	8 (2.0)	31.83 (7.8)
IR (per 100 PY)	1.7	4.6

SOURCE: CSR Table 14.2.1; Reviewer analysis of ADaM dataset (ADTTE)

STUDY 747-405: OUTLINE

- Study design, data sources, and methods
- Key study results
- **Data relevance and reliability**

STUDY 747-405: Data Relevance and Reliability (1)



- Data with complex provenance that appears traceable
- Data of undetermined accuracy and completeness
 - PBC
 - UDCA Treatment Failure
 - History of hepatic decompensation
 - Covariates
 - Clinical outcomes

STUDY 747-405: Data Relevance and Reliability (2)



- Data of undetermined accuracy and completeness
 - PBC / UDCA Treatment Failure / No history of hepatic decompensation
- Artifactual association between OCA and PBC outcomes might be observed if errors identifying the OCA-indicated population (non-cirrhotic or compensated PBC failing UDCA)
 - occurred more often in one comparison group than another
 - described patients with different underlying expectation (or risk) for poor outcome

STUDY 747-405: Data Relevance and Reliability (3)

- Data of undetermined accuracy and completeness
 - Exclusion criteria / Covariates
- A favorable determination about the adequacy of weighting methods used to achieve comparability between treated and control requires confidence in the
 - accuracy and completeness of the information used to exclude patients with non-PBC reasons for abnormal ALP or BILI
 - ability of measured covariates to capture differences in prognosis fully and accurately

STUDY 747-405: Data Relevance and Reliability (4)



- Data of undetermined accuracy and completeness
 - Death and liver transplantation
- Missing information about
 - Datavant tokens and matching algorithms
 - Information about the quality of underlying PII in source data
 - specific information about the accuracy of matches

STUDY 747-405: Data Relevance and Reliability (5)

- Undetermined accuracy and completeness
 - hepatic decompensation (false or true positive)
- Codes not validated in patients who fulfilled eligibility criteria
- Regulatory context creates expectation for strong methods to distinguish true positive incident hepatic decompensation events from other (false positive) possibilities
- Outcomes not adjudicated, verified, or validated against medical records

STUDY 747-405: Data Relevance and Reliability (6)



- Undetermined accuracy and completeness
 - hepatic decompensation outcome
- Differential outcome misclassification

STUDY 747-405: Data Relevance and Reliability (7)

Validation Studies in Medical Literature					
Author Year	Population	Data Source	Reference Standard (Outcomes)	Algorithm	Performance
Lo Re 2011	HIV	Veterans Administration	ascites, SBP, or variceal bleed	≥1 inpatient or ≥2 outpatient ICD-9 codes	71% PPV
Goldberg 2012	cirrhosis	UPHS	hepatic decompensation	≥1 ICD-9 code	90% PPV
Kanwal 2012	cirrhosis	Veterans Administration	gastrointestinal bleeding	≥1 inpatient ICD-9 code	83% PPV 89% NPV
			ascites	≥1 ICD-9 code	93% PPV 77% NPV
			hepatic encephalopathy	≥1 ICD-9 code	86% PPV 87% NPV
Lapointe-Shaw 2018	liver clinic	Ontario, Canada	hepatic decompensation	≥1 inpatient diagnosis	90% Sensitivity 88% Specificity
Mapakshi 2018	cirrhosis	Veterans Administration	ascites	≥1 ICD-10 code	88% PPV
Bengtesson 2020	chronic liver disease	Swedish National Patient Register	ascites	≥1 inpatient or specialized outpatient ICD-10 code	93% PPV
Hayward 2020	cirrhosis	Tertiary hospital in Australia	ascites	≥1 inpatient ICD-10 code	97% PPV 76% NPV
			esophageal varices with bleeding	≥1 inpatient ICD-10 code	100% PPV 58% NPV
			hepatic encephalopathy	≥1 inpatient ICD-10 code	55% PPV 78% NPV

STUDY 747-405: Data Relevance and Reliability (8)



- Misalignment between observation window and therapeutic effect expected from OCA on clinical outcomes

STUDY 747-405: Epidemiology Concerns

- Accuracy and completeness of study variables (inclusion/exclusion criteria, covariates, and outcomes)
- Inferential error due to uncontrolled confounding and outcome misclassification
- Insufficient follow-up for long latency outcomes
- Differential censoring possibly leading to post-baseline non-comparability between OCA treated and control

Statistical Analysis of Observational Cohort Study 747-405

Eugenio Andraca-Carrera, CDER/OTS/OB/DB7 (Presenter)

Ed Bein, CDER/OTS/OB/DB7

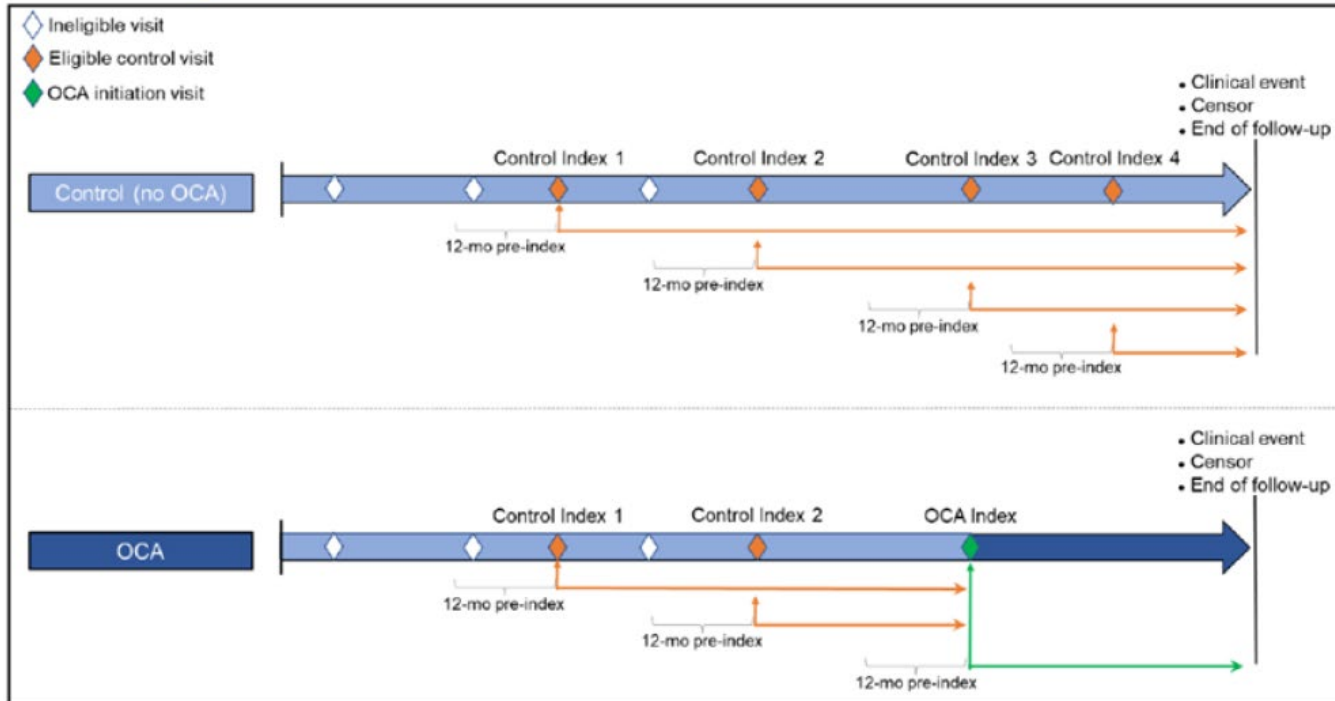
Ki Chung, CDER/OTS/OB/DAI



Outline

- 747-405 Study design
- Applicant's analyses
- Additional Analyses Conducted by FDA Review Team

Treatment Decision Design



OCA=obeticholic acid

Number of Patients and Indices

	OCA	Control (Unweighted)	Control (Weighted)
Patients¹	403	4174	-
Indices	403	11246	405.37

¹ 196 patients contributed both an OCA index and at least 1 Control index. These patients are included in both OCA and Control columns of this table.



Outline

- 747-405 Study design
- **Applicant's analyses**
- Additional Analyses Conducted by FDA Review Team

Applicant's Primary Analysis

- Primary endpoint: time to hepatic decompensation, liver transplant or death
- Censoring rules are based on “As-treated” follow-up (also known as While on Treatment)
- Control indices are weighted to make the control cohorts comparable to the OCA indices (population of interest)
- Bootstrap 95% confidence intervals adjust for the use of multiple indices per patients
- The Applicant also conducted “ITT-1” and “ITT-2” analyses that remove some of the censoring rules of the “As-treated” analysis

Censoring Rules



CRITERION	<u>AS-TREATED</u>	
	OCA	Control
OCA end	✓	
OCA start		✓
Fibrate start	✓	✓
UDCA restart		✓
Closed claims end	✓	✓
Study end	✓	✓

Source: Applicant’s Clinical Study Report

Censoring Rules



	<u>AS-TREATED</u>		<u>ITT-1</u>	
CRITERION	OCA	Control	OCA	Control
OCA end	✓			
OCA start		✓		✓
Fibrate start	✓	✓	✓	✓
UDCA restart		✓		✓
Closed claims end	✓	✓	✓	✓
Study end	✓	✓	✓	✓

Source: Applicant’s Clinical Study Report

Censoring Rules



	<u>AS-TREATED</u>		<u>ITT-1</u>		<u>ITT-2</u>	
CRITERION	OCA	Control	OCA	Control	OCA	Control
OCA end	✓					
OCA start		✓		✓		
Fibrate start	✓	✓	✓	✓	✓	✓
UDCA restart		✓		✓		
Closed claims end	✓	✓	✓	✓	✓	✓
Study end	✓	✓	✓	✓	✓	✓

Source: Applicant's Clinical Study Report

Results of Applicant's Analyses

Time to Hepatic Decompensation, Liver Transplant, or Death

Analysis Method	OCA N=403		Controls N=405.37 (weighted)		Treatment Effect	
	events	IR	events	IR	HR	95% CI
As-treated	8	1.7	31.8	4.6	0.37	0.14, 0.75
ITT-1	22	2.8	31.8	4.6	0.59	0.34, 0.99
ITT-2	22	2.8	34.0	4.3	0.64	0.38, 1.05

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

Source: Applicant's Analyses, reproduced by FDA review team



Informative Censoring

As-treated analysis is likely subject to informative censoring.

- ITT-1 and ITT-2 may also experience this issue (they are censored for start of fibrates or end of closed claims)

Informative Censoring: High Treatment Discontinuation in the As-Treated Analysis

Event	Treated with OCA N=403		Controls (Weighted) N=405.37	
	n	%	n	%
Primary endpoint	8	2.0%	31.83	7.9%
Treatment switch	215	53.3%	85.37	21.1%
OCA end	196	48.6%	-	-
Fibrate start	19	4.7%	11.18	2.8%
OCA start	-	-	50.03	12.3%
UDCA restart	-	-	24.16	6.0%
Closed claims end	73	18.1%	91.27	22.5%
Study end	107	26.6%	196.9	48.6%

*Source: table produced by FDA review team



Informative Censoring: High Treatment Discontinuation in the As-Treated Analysis

Event	Treated with OCA N=403 Mean follow-up: 436 days		Controls (Weighted) N=405.37 Mean follow-up: 627 days	
	n	%	n	%
Primary endpoint	8	2.0%	31.83	7.9%
Treatment switch	215	53.3%	85.37	21.1%
OCA end	196	48.6%	-	-
Fibrate start	19	4.7%	11.18	2.8%
OCA start	-	-	50.03	12.3%
UDCA restart	-	-	24.16	6.0%
Closed claims end	73	18.1%	91.27	22.5%
Study end	107	26.6%	196.9	48.6%

*Source: table produced by FDA review team

Informative Censoring:

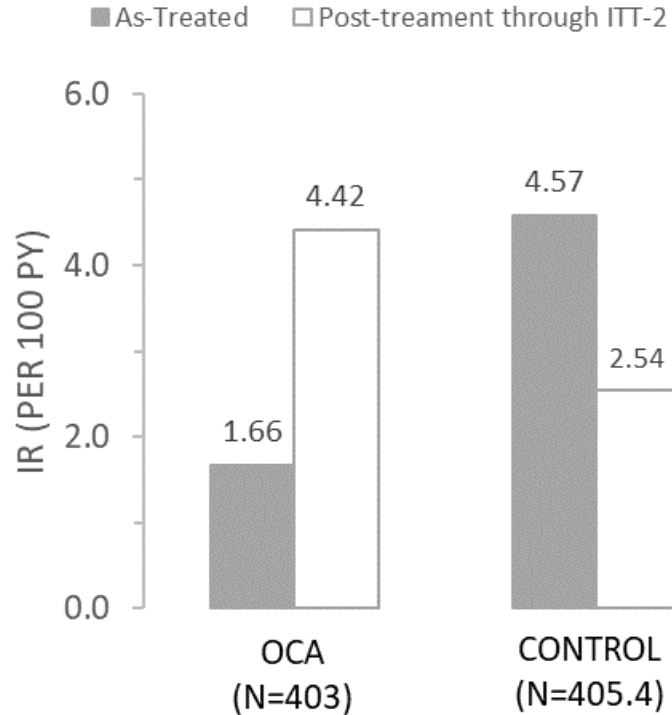
Hepatic AEs Are Associated With Discontinuation of Ocaliva®

Monitoring for Safety, Treatment Discontinuation (2.3)

- Routinely monitor all patients for progression of PBC disease.
- Reduce the dosing frequency for patients who progress from Child-Pugh Class A to Child-Pugh Class B or C. (2.2)
- Closely monitor patients at an increased risk of hepatic decompensation.
- Interrupt treatment in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor liver function.
- Consider discontinuing OCALIVA in patients who experience clinically significant liver-related adverse reactions.

*Source: USPI February 2018

Informative Censoring: Incidence Rates During and After the As-Treated Censoring



*Source: Figure produced by FDA review team



Outline

- 747-405 Study design
- Applicant's analyses
- **Additional Analyses Conducted by FDA Review Team**

FDA Additional Analyses

- ITT-like analysis of time to liver transplant or death (excluding hepatic decompensation)
- Patient indices are followed from study entry until the earliest of an event or End of Study (12/31/2021)
 - This analysis does not censor for fibrate start or end of closed claims

Analyses of Time to Liver Transplant or Death

Analysis Method	OCA N=402		Controls N=404.55 (Weighted)		Treatment Effect	
	Events	IR	Events	IR	HR	95% CI
As-Treated	2	0.41	11.97	1.67	0.27	0.0 – 0.93
ITT-1	13	1.6	11.97	1.67	0.92	0.43 – 1.86
ITT-2	13	1.6	12.72	1.5	1.07	0.49 – 2.07
FDA ITT	19	1.64	22.09	1.96	0.80	0.45 – 1.38

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

- 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. The table in this slide excludes these 58 patients. Earlier slides were based on results that include these 58 patients.
- Source: analyses conducted by the FDA review team

Conclusions for Study 747-405

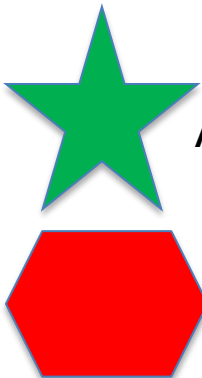
- FDA identified concerns about the relevance and reliability of the data
- Applicant's As-Treated Analysis is likely subject to informative censoring
- Analyses of death + liver transplant (ITT-1, ITT-2, FDA ITT) do not demonstrate efficacy

Charge to the Advisory Committee

sNDA 270999-Ocaliva[®] (OCA) for the Treatment of Primary Biliary Cholangitis
(PBC)

Frank A Anania, MD
Acting Director, Division of Hepatology and Nutrition (DHN)
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

sNDA 207999 Aims to Fulfill Accelerated Approval for NDA 207999



Accelerated approval **May 2016**

Applicant proposes and submits RWE

Contraindication statement and amended box warning, **May 2021**, restricted eligibility for OCA use in patients with PBC.

Applicant and Agency Positions for the Two Studies: Interpretability



Study	Applicant Position	Agency Position
747-302 (R DB PC)	Not Interpretable (functional unblinding, treatment crossover, and USPI labeling changes in May 2021)	Interpretable (provides safety and efficacy data for product in a controlled setting for the ITT and USPI-labeled populations)
747-405 (RWE)	Interpretable	Not interpretable (Data of undetermined reliability and accuracy)

RWE, real world evidence
R DB PC, randomized double-blind placebo-controlled

Applicant and Agency Positions: Clinical Benefit

Study	Applicant Position	Agency Position
747-302 (R DB PC)	Clinical benefit cannot be assessed to verify Study 747-301 (<i>pivotal trial data granting accelerated approval</i>)	Clinical benefit not demonstrated to verify Study 747-301
747-405 (RWE)	Confirms clinical benefit of Study 747-301 and fulfills accelerated approval requirement	Data with questionable relevance and reliability. Study was not adequate and well-controlled to confirm clinical benefit.

RWE, real world evidence

R DB PC, randomized double-blind placebo-controlled

Applicant and Agency Positions: Safety

Study	Applicant Position	Agency Position
747-302 (R DB PC)	No conclusion concerning safety	Imbalance in the of number of liver transplants in the USPI-labeled population compared to the placebo USPI-labeled treatment cohort
747-405 (RWE)	Study supports adequate safety for OCA use in the USPI-labeled population	Study not designed to characterize safety

RWE, real world evidence

R DB PC, randomized double-blind placebo-controlled

Core Issues Summary (1)



- Although PBC remains an unmet medical need, when accelerated approval was granted for OCA, the landscape for PBC therapeutics for the intended-use population has changed in 2024.
 - *Clinical benefit for other newly approved agents has not yet been verified.*
- 747-302 did not demonstrate clinical effectiveness but provided safety data in the USPI-labeled population.
 - PBC is an indolent disease.
 - Imbalance in the number of subjects in the USPI-labeled cohort on OCA requiring transplant compared to the USPI-labeled cohort on placebo is unexpected.
- Hepatotoxicity has been a concerning safety signal for OCA which led to two boxed warnings for Ocaliva[®], the second of which contraindicated use in sicker PBC patients. A hepatotoxicity signal was also observed in the Applicant's studies of OCA for the treatment of metabolic-dysfunction associated steatohepatitis (MASH).

Core Issues Summary (2)



- The Applicant asserts Study 747-405 fulfills the requirement to demonstrate clinical benefit of Ocaliva[®] as a safe and effective treatment for the intended-use population (USPI-labeled population).
- The Agency's assessment is that Study 747-405 is inadequate and not well-controlled to demonstrate clinical effectiveness.

Discussion Questions for the AC

1. Discuss whether the evidence generated post-approval verify the benefit of obeticholic acid (OCA, Ocaliva®) on clinical outcomes (hepatic decompensation, liver transplant, and death) in adults with PBC? Specifically, discuss the evidence generated in the:
 1. Post-marketing required Study 302, and
 2. Observational Study 405
2. Discuss the safety of OCA, including the incidence of liver transplant and all-cause death in the United States Prescribing Information (USPI)-labeled and the overall study population.



Voting Questions for the AC

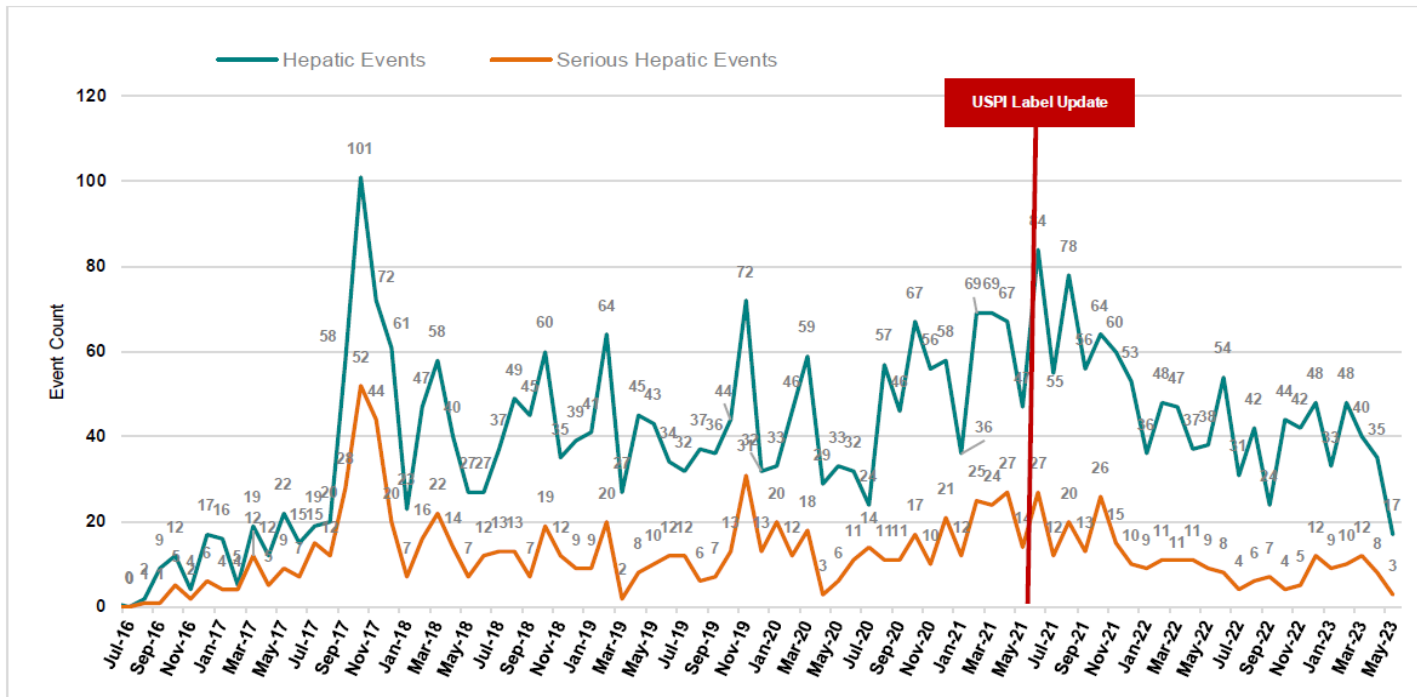
1. Does the available evidence verify the benefit of OCA on clinical outcomes (hepatic decompensation, liver transplant, and death) in the USPI-labeled population? Provide a rationale for your vote.
2. Is the benefit-risk profile of OCA favorable in the USPI-labeled population? Provide a rationale for your vote.



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BACK-UP SLIDES SHOWN

2023 Postmarketing Reporting



Source: Applicant's Postmarketing Summary 2023 Submission (Module 5.3.6) to NDA 207999, Page 23 of 28

Baseline Disease Characteristics, Trial 747-302

Characteristic	USPI-Labeled		USPI-Contraindicated		ITT Population	
	OCA	Placebo	OCA	Placebo	OCA	Placebo
	N=81 n (%)	N=68 n (%)	N=87 n (%)	N=98 n (%)	N=168 n (%)	N=166 n (%)
Cirrhosis group, n(%)						
Non-cirrhotic	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 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)
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)
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%)

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

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