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

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

## FDA Introductory Remarks

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Division of Hepatology and Nutrition (DHN)
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# 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

Ursodeoxycholic acid, December 1997
Ocaliva, May 2016
Iqirvo, June 2024
Livdelzi , August 2024

# Obeticholic Acid (OCA)

- Ocaliva® (obeticholic acid, or OCA)
  - Synthetic derivative of chenodeoxycholic acid (6α-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

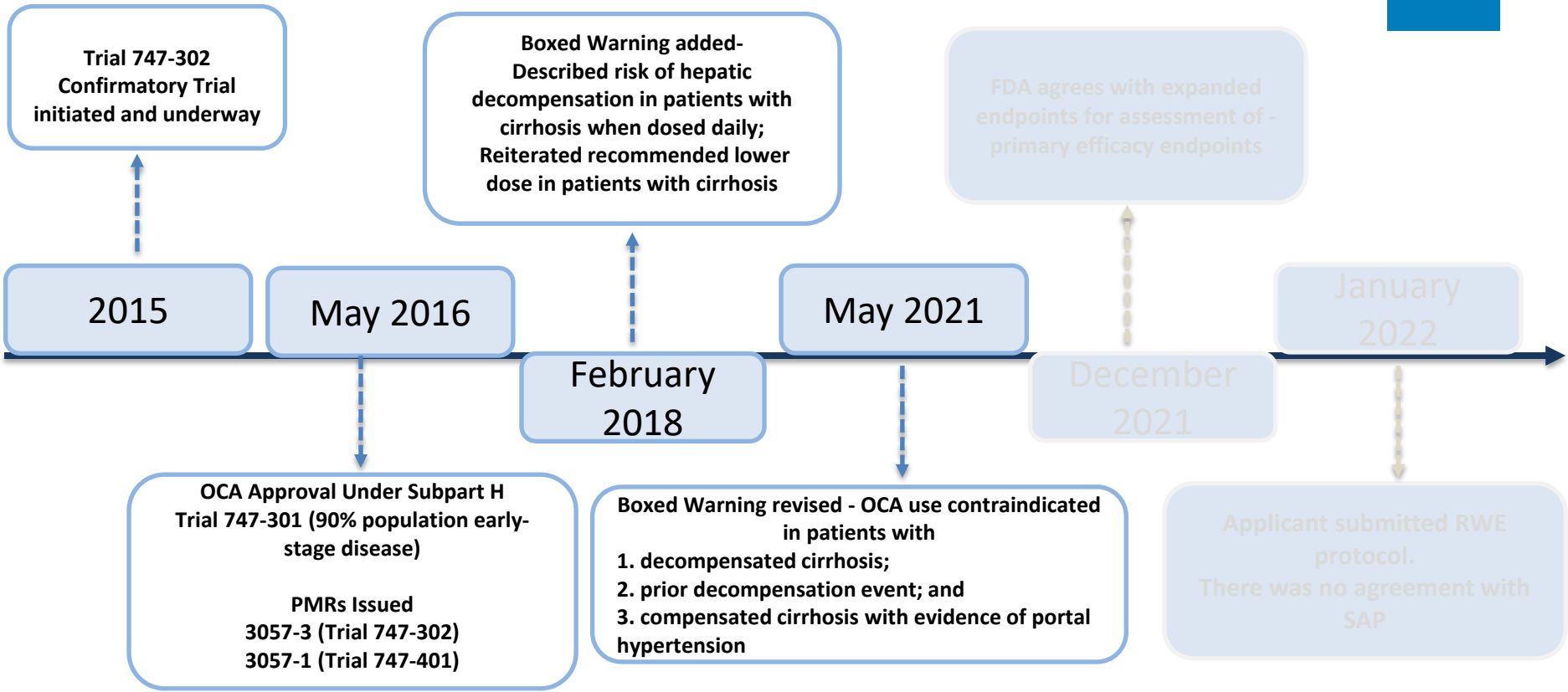
# Regulatory Framework for Drug Approval

- 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




Abbreviations: PMR, post-marketing required study; RWE, real world evidence; SAP, statistical analysis plan

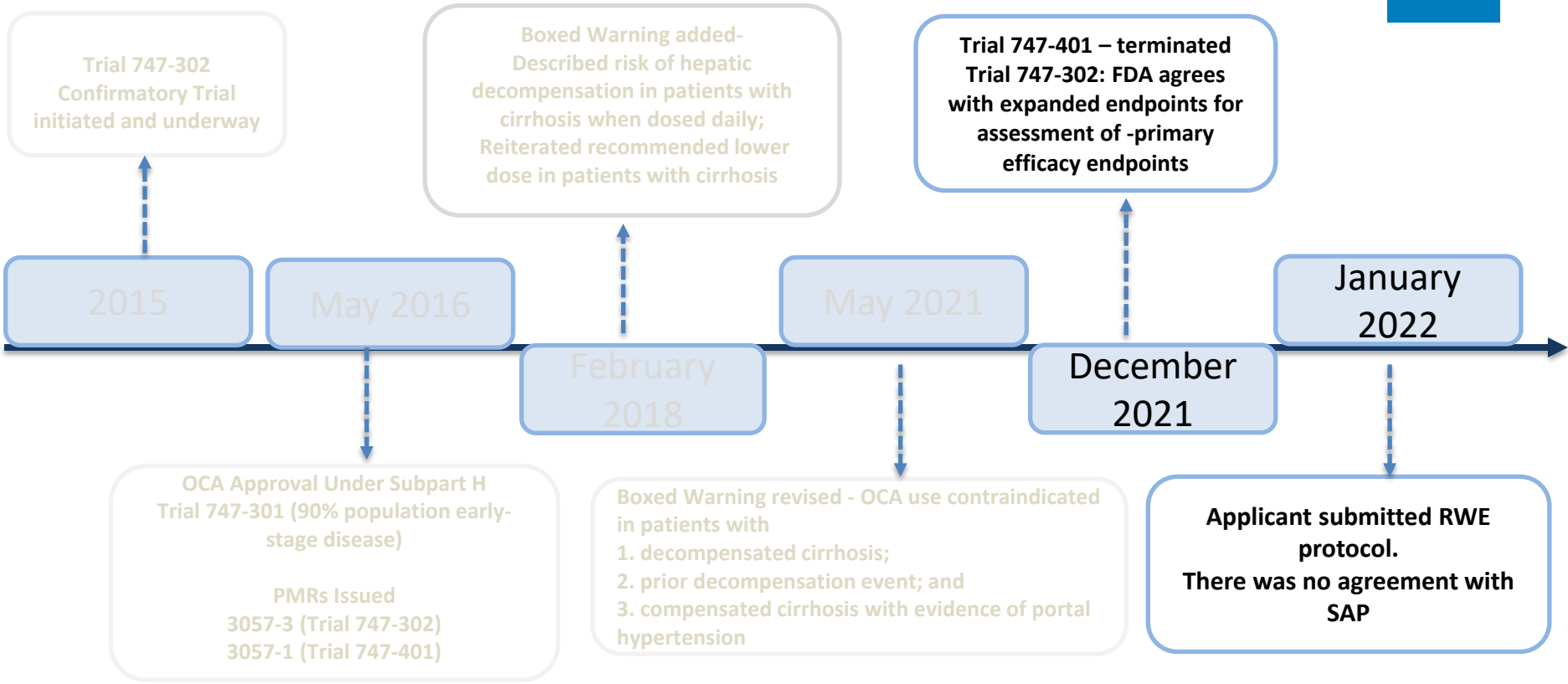
# Safety Labeling Changes

- **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*

*February 2018; May 2021*

# Regulatory History




Abbreviations: PMR, post-marketing required study; RWE, real world evidence; SAP, statistical analysis plan

# 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.

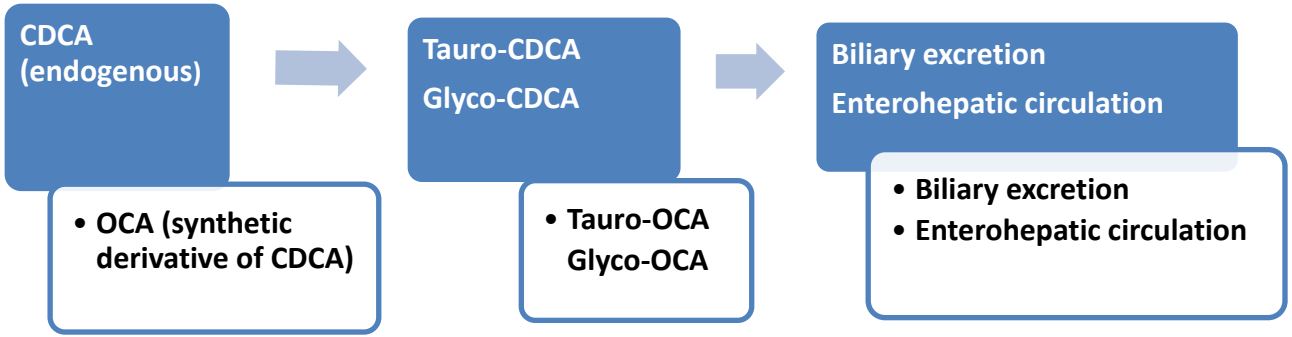
2. Is the benefit-risk profile of OCA favorable in the USPI-labeled population? Provide a rationale for your vote.

# 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

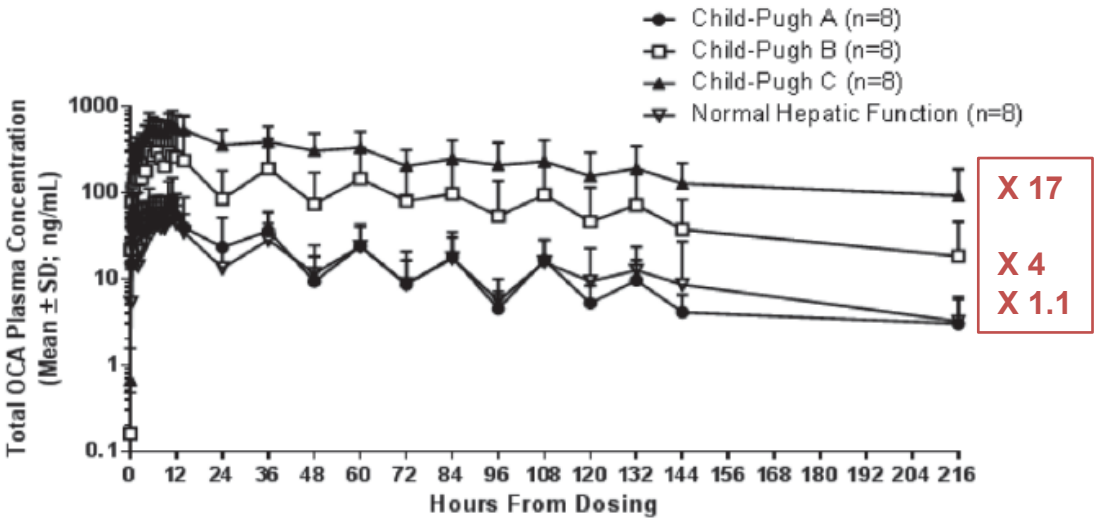



- Major active conjugates with substantially higher exposure than OCA
  - Long half-life
  - Substantial exposure accumulation following multiple doses
  - Systemic exposure presented as total OCA concentration (= OCA + Tauro-OCA + Glyco-OCA)

- **Liver dysfunction significantly affects the pharmacokinetics (PK) of OCA and its major conjugates**

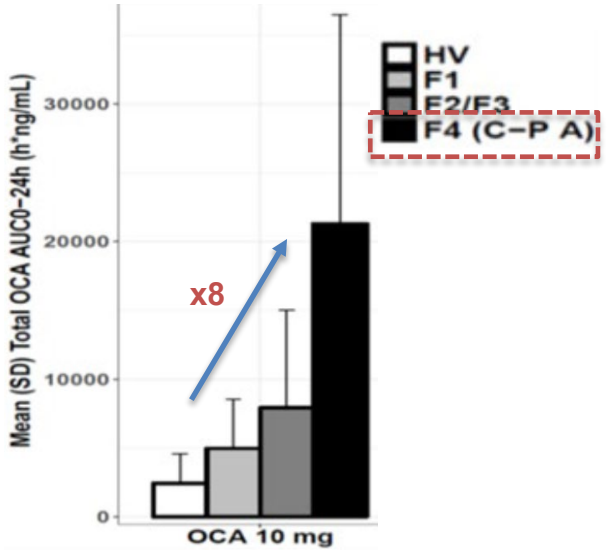
# Significant and Variable Impact of Hepatic Impairment (HI) on PK

Total OCA Concentrations Versus Time After Single-Dose Administration[1]




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

Total OCA Exposure at Steady-State[2]




PK variability within CP-A class

[1] Clinical Pharmacology Review of Original NDA 207999 (2016)

[2] FDA 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 HI[1]
- 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**

[1] Ocaliva USPI (May 2016)

# Planned and Studied Dosing Regimens in Study 302

## Number of Subjects in OCA Arm per Baseline Cirrhosis Status and USPI Status[1]

| 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)<br>19 (CP-B with CSPH*) |

* CSPH: clinically significant portal hypertension

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

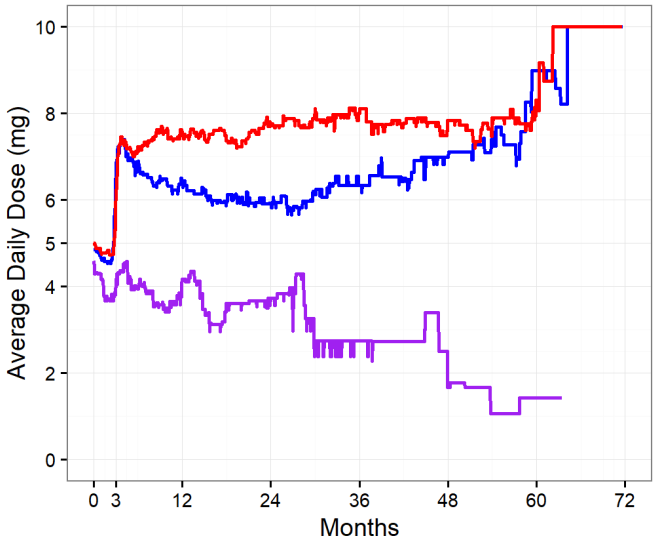
## Dosage Adjustment In USPI Labeled Population

- 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

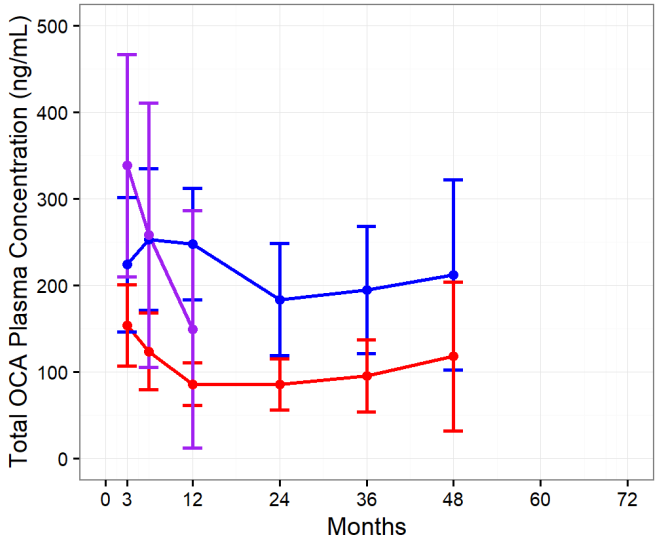
[1] Ocaliva USPI (May 2021)
[2] Protocol Version 3 (2017)

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

## Average Daily Dose



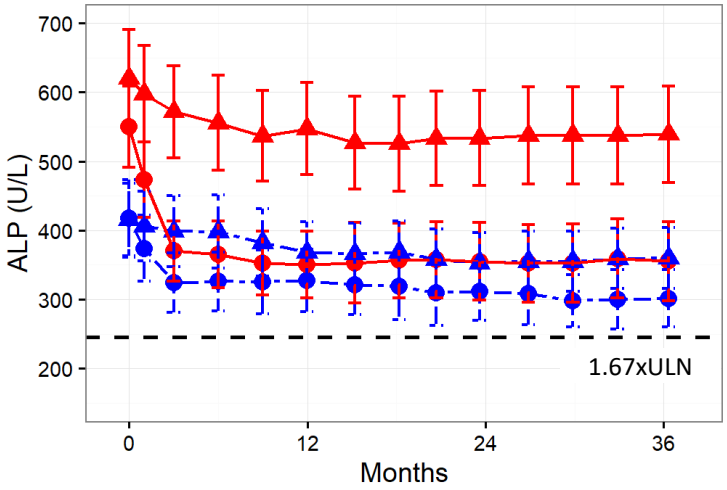

## Mean Trough Concentration

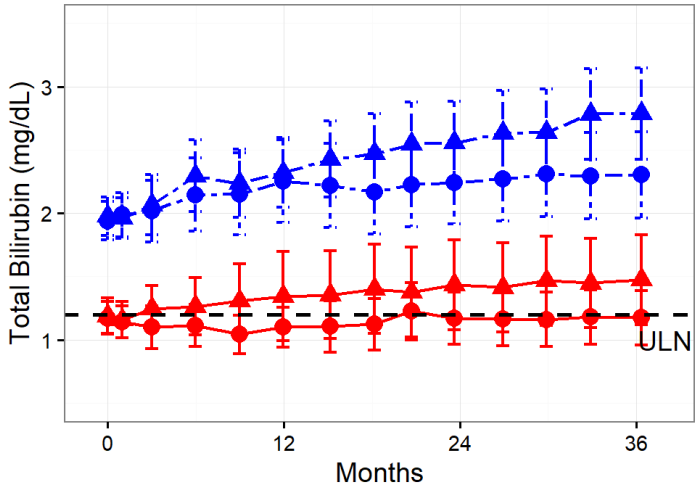



Compensated cirrhosis
Decompensated cirrhosis
Non-cirrhotic

**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 | 98 | 73 | 41 | 22 |
| OCA | 87 | 57 | 40 | 30 |

| | | | | |
|---|---|---|---|---|
| Placebo | 68 | 49 | 29 | 20 |
| OCA | 81 | 59 | 45 | 31 |

| | | | | |
|---|---|---|---|---|
| Placebo | 98 | 73 | 41 | 22 |
| OCA | 87 | 57 | 40 | 30 |

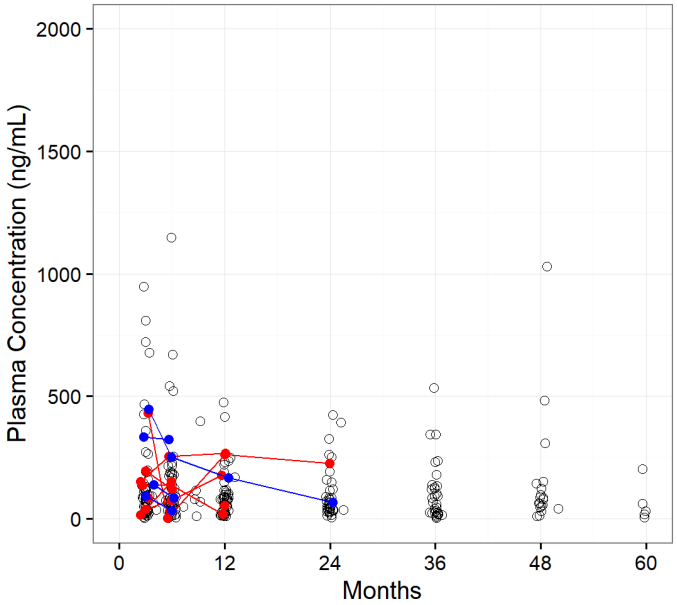
OCA USPI-contraindicated
Placebo USPI-contraindicated
OCA USPI-labeled
Placebo USPI-labeled

Missing value imputed by Last Observations Carried Forward (LOCF)
ULN: upper limit of normal

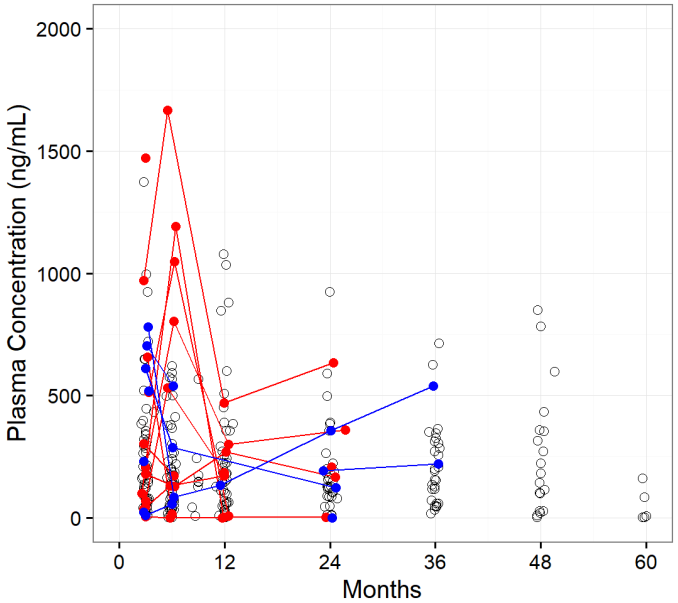
Study 302

# 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

Study 302

# 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 > 1.67xULN in both cohorts
- At month 12, the biochemical response[1] 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



[1] ALP < 1.67XULN, TB ≤ ULN, and ≥ 15% ALP decrease from baseline

# STUDY 747-302

**Tram Tran, MD FACG FAASLD (Presenter)**
Division of Hepatology and Nutrition (DHN)
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Yura Kim, PhD CDER/OTS/OB/DBIII
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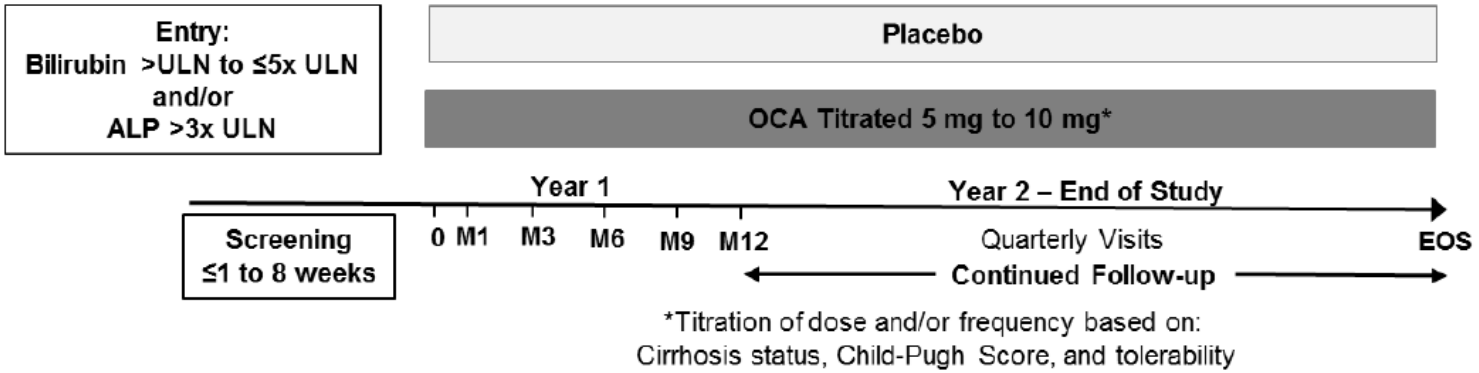
# STUDY 747-302

- 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

| *All subjects (events are denoted "Group 1 events")* |
|---|
| • **Death (all-cause)**<br>• **Liver transplant**<br>• **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:**<br>  ○ **Variceal bleed**<br>  ○ **Hepatic encephalopathy** (as defined by a West Haven score of ≥2)<br>  ○ **Spontaneous bacterial peritonitis** (confirmed by diagnostic paracentesis OR presence of >250/mm$^3$ polymorph leukocyte [PMNs] in the ascitic fluid)<br>  ○ Bacterial empyema (confirmed by diagnostic thoracentesis OR presence of >250/mm$^3$ PMNs in the pleural fluid)<br>• **Uncontrolled or refractory ascites** (requiring large volume paracentesis)<br>• Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club , portopulmonary syndrome, or hepatopulmonary syndrome)<br>• MELD-Na score ≥15 (for subjects with baseline MELD-Na score <12)<br>• **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<br>• Hepatic encephalopathy requiring lactulose and/or rifaximin<br>• 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)<br>• Platelets <150 x 10$^9$/L with splenomegaly and/or with transient elastography >15 kPa |

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 (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/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 , 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)

| *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<br>• Hepatic encephalopathy requiring lactulose and/or rifaximin<br>• 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)<br>• Platelets <150 x 109/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**

| | 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

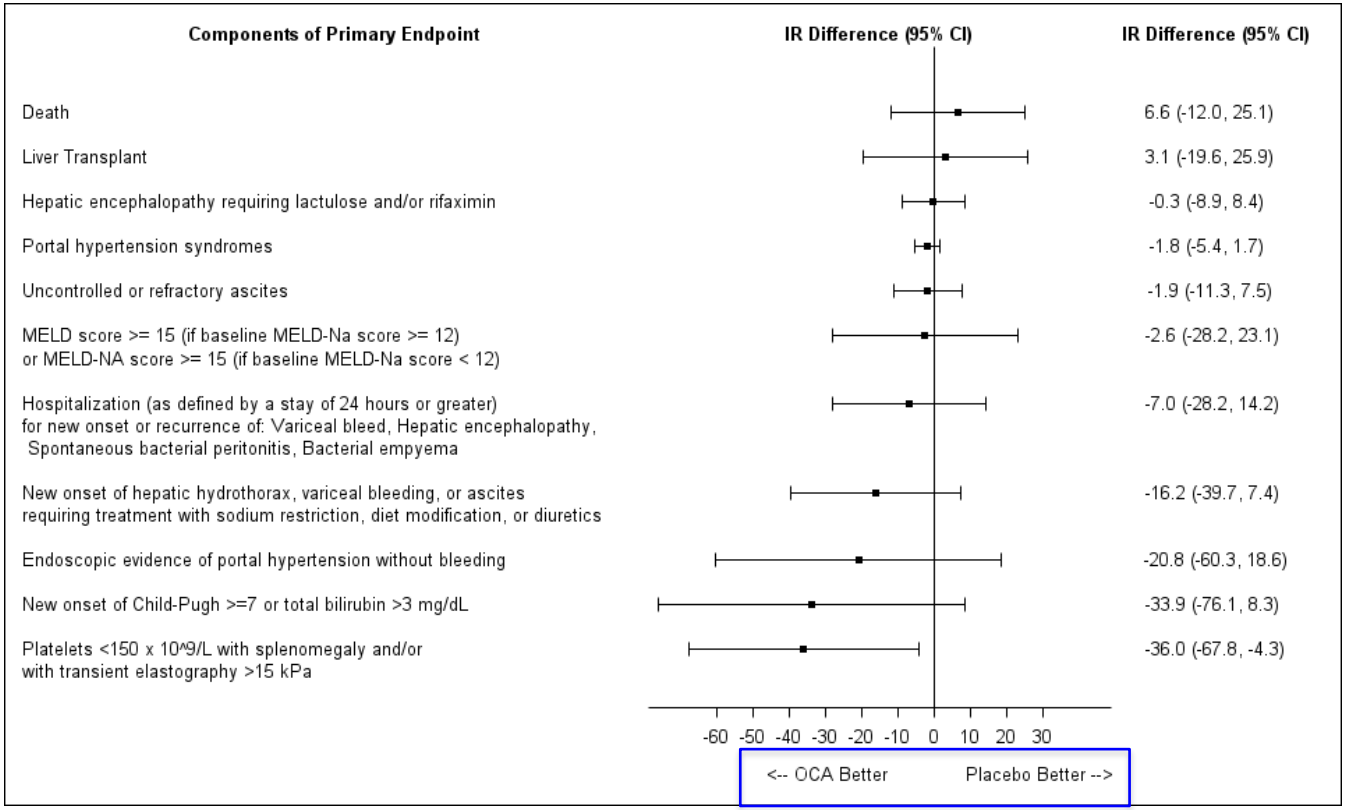
Abbreviations: OCA, Obeticholic Acid; N, number of subjects in treatment arm; n, number of subjects with given characteristic UDCA, ursodeoxycholic acid

- 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)

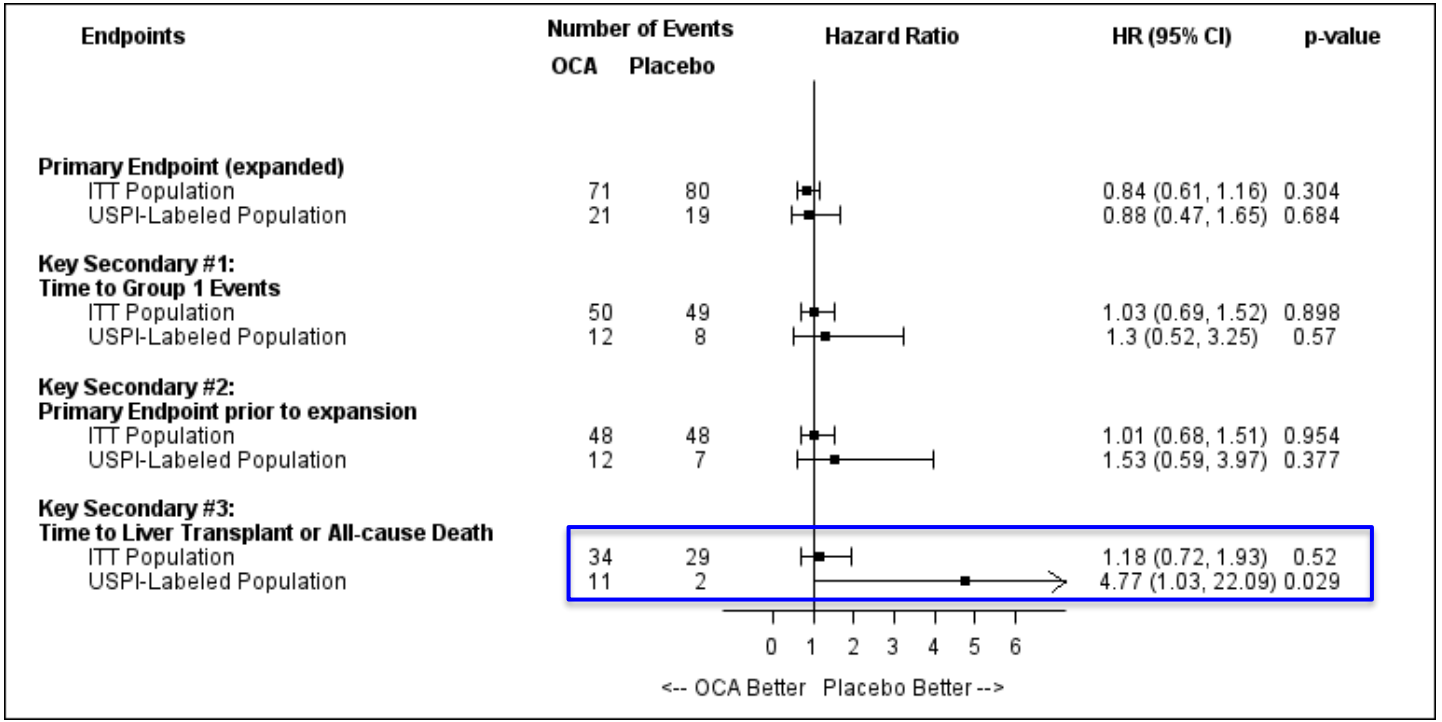



Source: Statistical reviewer analysis using Applicant submitted dataset adevt,xpt and adsl.xpt

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

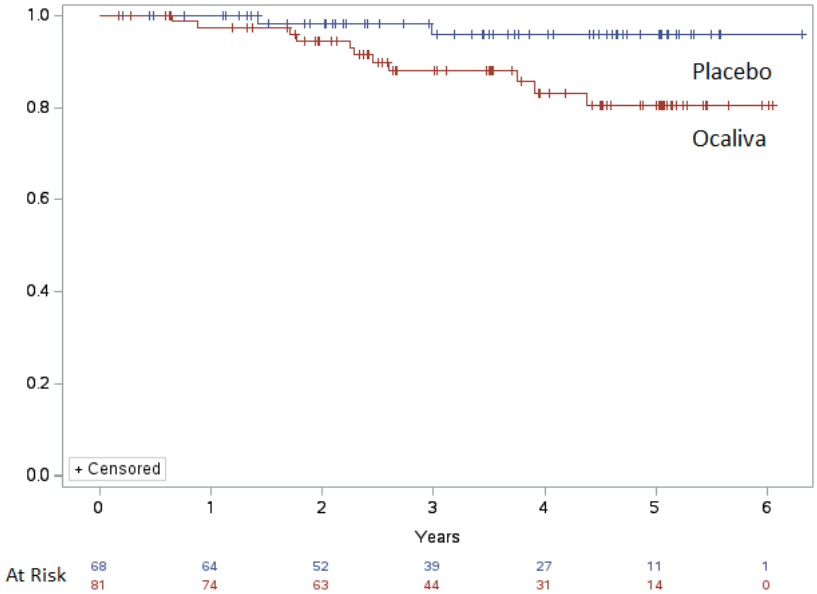



Source: Statistical reviewer's analysis using adtte.xpt and adsl.xpt; Results aside from key secondary endpoint #3 in ITT population match Applicant's results
Total sample size for ITT population: OCA, N=168; Placebo, N=166; Total sample size for USPI-labeled population: OCA, N=81; Placebo, N=68
The 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

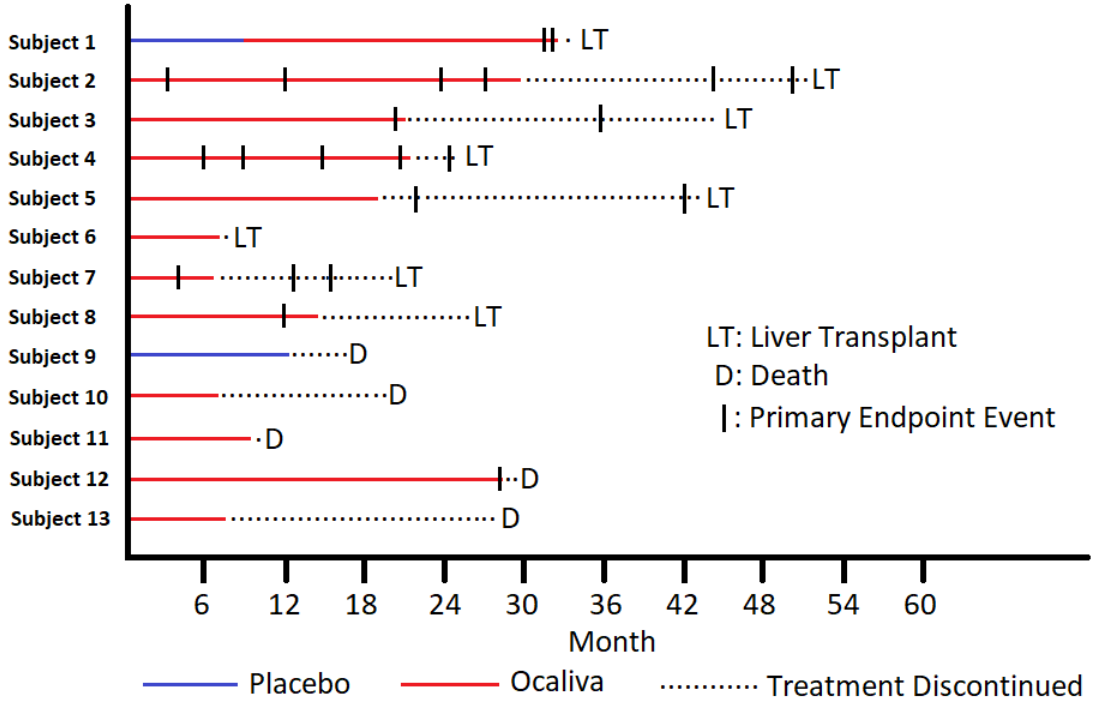
| Subject | Age /Sex | Treatment Arm | Cirrhosis Status at Baseline | Last Day IP /OLT Study Day | Review Findings |
|---|---|---|---|---|---|
| **Sub 1** | 47/F | Placebo* | Noncirrhotic | 268/1078<br>Commercial OCA: Days 269-985/1078 | Multiple **portal hypertensive bleeds**, **ascites**. |
| **Sub 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



Abbreviations: TB, total bilirubin; CP, Child Pugh; MELD, model for end-stage liver disease IP-investigational product, TB, total bilirubin, OLT, orthotopic liver transplant

# 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



cOCA: commercial OCA, GIB gastrointestinal bleed

# 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<br>Positive for esophagitis<br>chronic gastropathy<br>hiatal hernia | EGD : Large EV Hypertensive gastropathy<br>HOC Committee: **"Progression to cirrhosis"** HOC committee | | UTI:<br>drug holiday | | **Hospitalization for GIB** | **Death: Multiple UGIB, shock, cerebral edema.**<br>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: 10^9/L

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

# Study 747-302: DILI Assessments
# Overall, Contraindicated, USPI-Labeled Populations

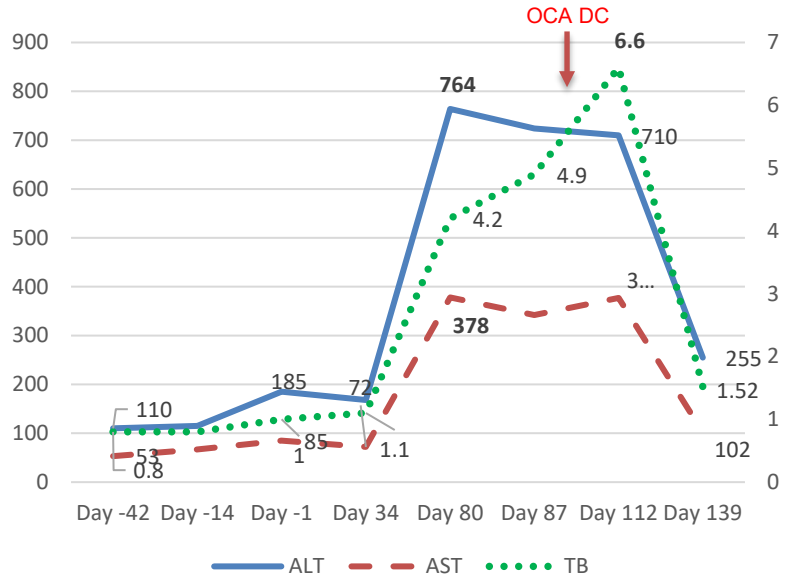
| HSAC DILI Adjudication | OCA | Placebo |
|---|---|---|
| | **Overall Safety Population n=168** | **Overall Safety Population n=166** |
| Probable DILI | 1 (0.59%) | 0 (0%) |
| Possible DILI | 17 (10%) | 8 (4.8%) |
| **TOTAL** | **18 (10.7%)** | **8 (4.8%)** |
| | **USPI-Contraindicated n=87** | **USPI-Contraindicated 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 |



Source: Applicant CSR,Hepatic Safety Adjudication Committee (HSAC) narrative page 568-574 747-302
HSAC Liver injury relatedness Adjudication pp 6220-6227 HSAC Endpoint Relatedness Adjudication pp 10591-10595

# 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

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

U.S. FOOD & DRUG ADMINISTRATION

# 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 [-∞,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

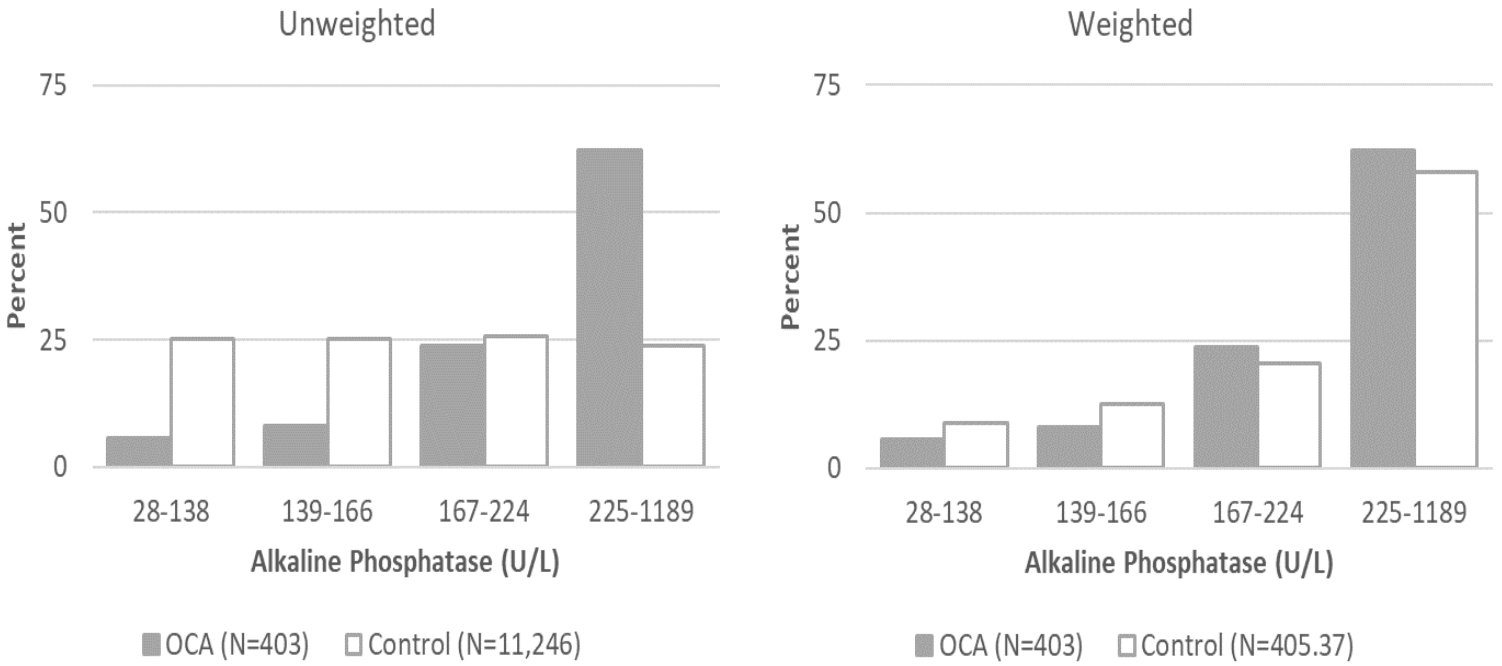
# STUDY 747-405: Key Study Result (1)

## 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 N=403 | Not Treated with OCA 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<br>89% NPV |
| | | | ascites | ≥1 ICD-9 code | 93% PPV<br>77% NPV |
| | | | hepatic encephalopathy | ≥1 ICD-9 code | 86% PPV<br>87% NPV |
| **Lapointe-Shaw 2018** | liver clinic | Ontario, Canada | hepatic decompensation | ≥1 inpatient diagnosis | 90% Sensitivity<br>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<br>76% NPV |
| | | | esophageal varices with bleeding | ≥1 inpatient ICD-10 code | 100% PPV<br>58% NPV |
| | | | hepatic encephalopathy | ≥1 inpatient ICD-10 code | 55% PPV<br>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

U.S. FOOD & DRUG ADMINISTRATION

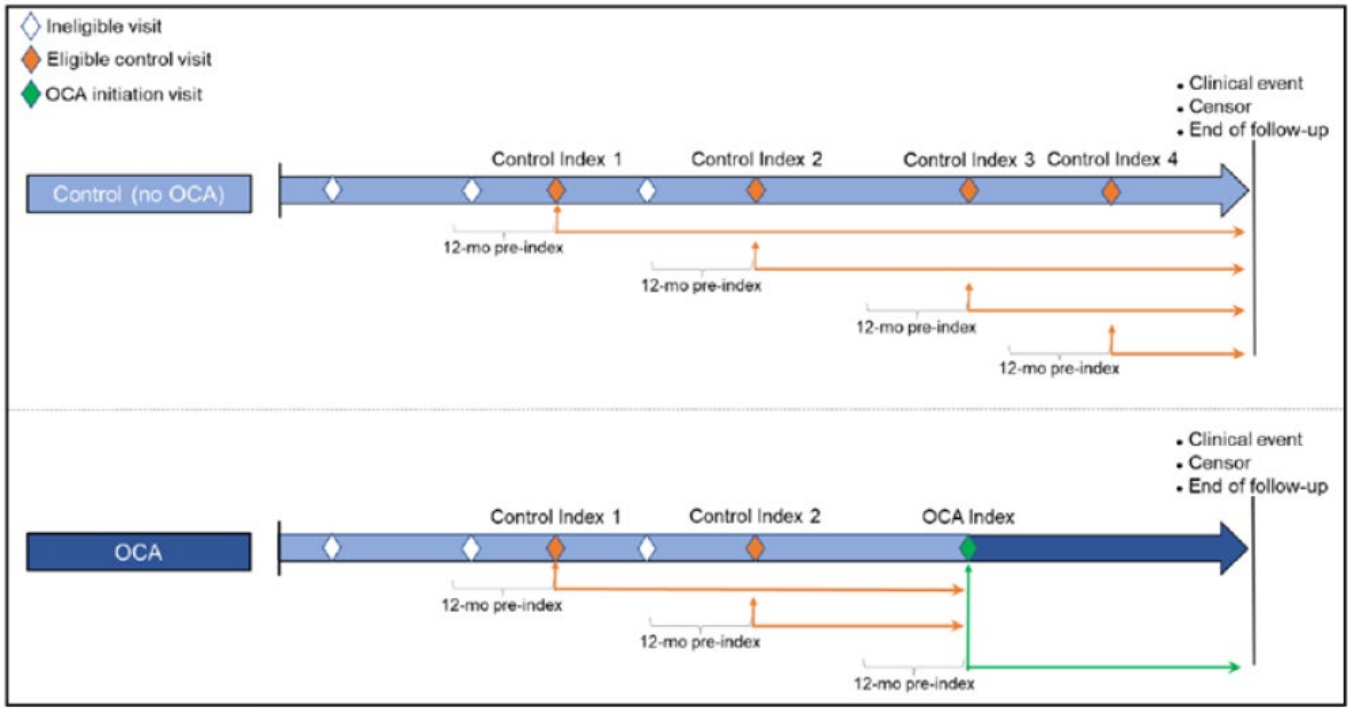
# Statistical Analysis of Observational Cohort Study 747-405

**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

Source: Applicant's Clinical Study Report

# Number of Patients and Indices

| | OCA | Control (Unweighted) | Control (Weighted) |
|---|---|---|---|
| **Patients**[1] | 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

| | AS-TREATED | |
|---|---|---|
| **CRITERION** | **OCA** | **Control** |
| OCA end | ✓ | |
| OCA start | | ✓ |
| Fibrate start | ✓ | ✓ |
| UDCA restart | | ✓ |
| Closed claims end | ✓ | ✓ |
| Study end | ✓ | ✓ |

Source: Applicant's Clinical Study Report

# Censoring Rules

| | AS-TREATED | | ITT-1 | |
|---|---|---|---|---|
| **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

| | AS-TREATED | | ITT-1 | | ITT-2 | |
|---|---|---|---|---|---|---|
| **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

| | Treated with OCA N=403 Mean follow-up: 436 days | | Controls (Weighted) N=405.37 Mean follow-up: 627 days | |
|---|---|---|---|---|
| **Event** | 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

| | Treated with OCA | | Controls (Weighted) | |
|---|---|---|---|---|
| | N=403 | | N=405.37 | |
| | Mean follow-up: 436 days | | Mean follow-up: 627 days | |
| **Event** | 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

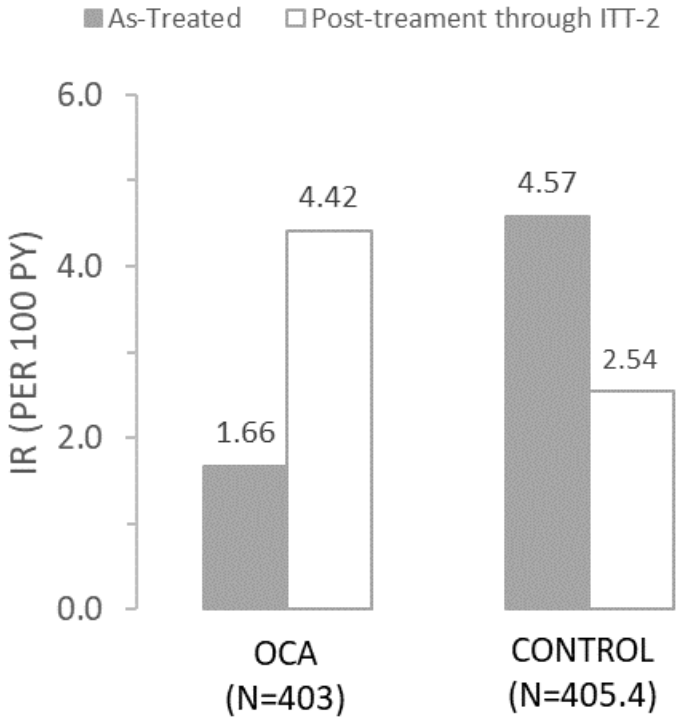
# Informative Censoring:
# Hepatic AEs Are Associated With Discontinuation of Ocaliva®

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

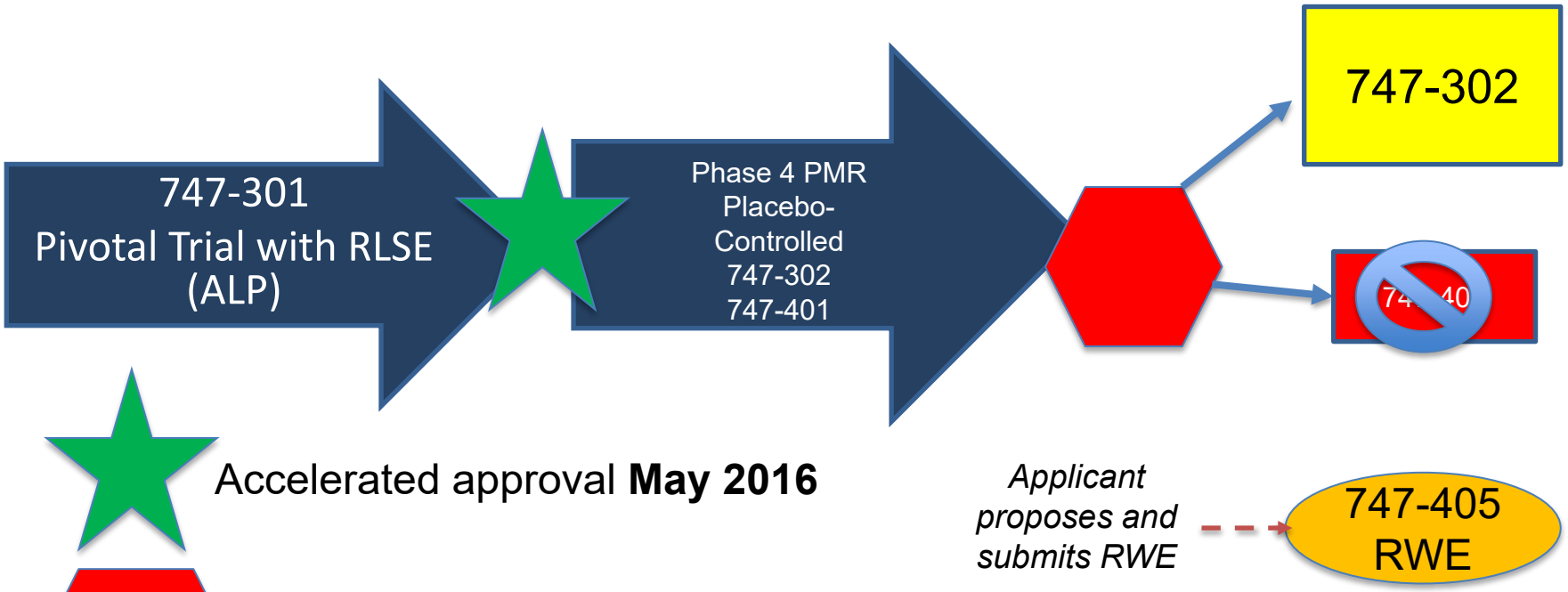
- FDA identified concerns about the relevance and reliability of the data
- Applicant's As-Treated Analysis is likely subject to informative censoring
- Analyses of death + liver transplant (ITT-1, ITT-2, FDA ITT) do not demonstrate efficacy

# 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






RLSE, reasonably likely surrogate endpoint that predicts clinical benefit
PMR, post-marketing required study

# 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 (*pivotal trial data granting accelerated approval*) | 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.
- Hepatoxicity 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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