U.S. FOOD & DRUG ADMINISTRATION

Obeticholic Acid for the Treatment of Adult Patients with Pre-cirrhotic Liver Fibrosis due to Non-Alcoholic Steatohepatitis (NASH)

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
May 19th, 2023

FDA Introductory Remarks

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Nonalcoholic Steatohepatitis

- NASH is a severe form of nonalcoholic fatty liver disease (NAFLD)
  - Characterized by the presence of fat, inflammation, and hepatocyte ballooning on liver histology
  - Patients are at risk of developing fibrosis and cirrhosis
  - Increasing fibrosis is associated with mortality
  - Associated with type 2 diabetes (T2D), dyslipidemia, hypertension, and obesity
- NASH prevalence is estimated ~16.8 million people in the U.S.
  - 5.7 million expected to have NASH with Stage 2 or 3 fibrosis
- NASH has an unmet medical need
  - There are no FDA approved treatments for NASH in the U.S.

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Obeticholic Acid

- Obeticholic acid (OCA) is a synthetic derivative of chenodeoxycholic acid
- OCA is a farnesoid X receptor (FXR) agonist
  - FXR is a nuclear receptor
    - Regulates bile acid biosynthesis
    - Affects metabolic pathways (glucose and lipid regulation)
    - Promotes cholesterol saturation in bile; increases risk of gallstone formation
- Less polar than endogenous bile acids (promotes gallstone formation)
- In a NASH model of diet-induced fatty liver disease in mice, OCA demonstrated improvement in liver inflammation and fibrosis

Applicant's Proposed Indication and Doses

- Applicant's Proposed Indication:
  - Treatment of adult patients with pre-cirrhotic liver fibrosis due to Nonalcoholic Steatohepatitis (NASH)
- Proposed Dosage Regimen:
  - OCA 25 mg, orally, once a day

Approval Pathways

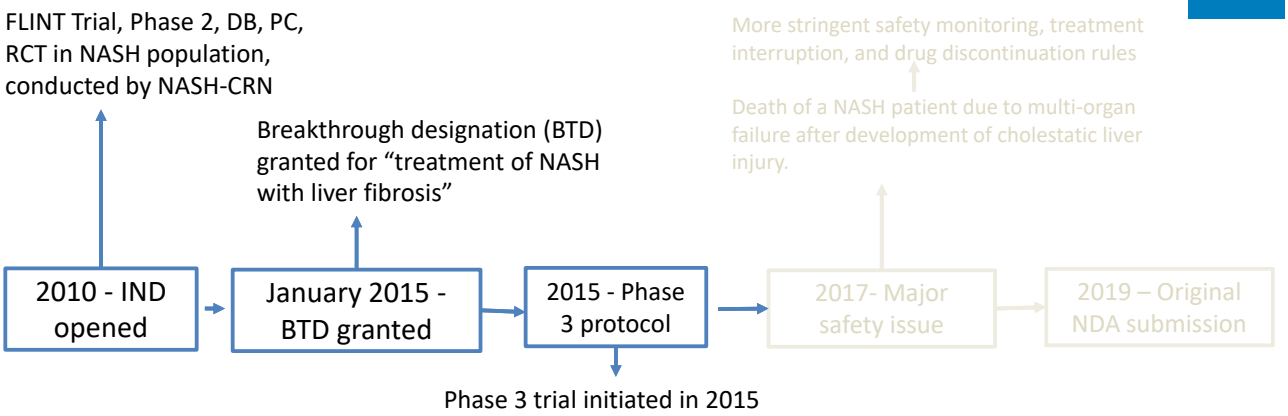
- Traditional Approval
  - Can be based on a clinical endpoint—how a patient feels, functions, or survives (i.e., reduced mortality)
  - Or validated surrogate endpoints (e.g., systolic blood pressure, HCV-RNA, LDL-C)
- Accelerated Approval
  - Allows for earlier approval of drugs to fill an unmet medical need for a serious condition
  - Can be based on a surrogate endpoint that is "reasonably likely to predict clinical benefit"

Surrogate Endpoints in Non-Cirrhotic NASH

- Surrogate endpoints considered reasonably likely to predict clinical benefit in NASH with stage 2 or 3 fibrosis*:
  1. Improvement of fibrosis by ≥1 stage AND no worsening of NASH (defined as no worsening of ballooning, lobular inflammation, or steatosis), OR
  2. Resolution of NASH AND no worsening of fibrosis (NASH resolution defined as 0 for ballooning, 0-1 for inflammation)
- An Applicant can demonstrate efficacy on either endpoint or both endpoints

*FDA, 2018, Guidance for Industry; Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment | FDA

Regulatory History 2010 - 2015



IND, Investigational New Drug Application
BTD, Breakthrough Designation
FLINT, farnesoid X receptor ligand obeticholic acid in NASH treatment

www.fda.gov

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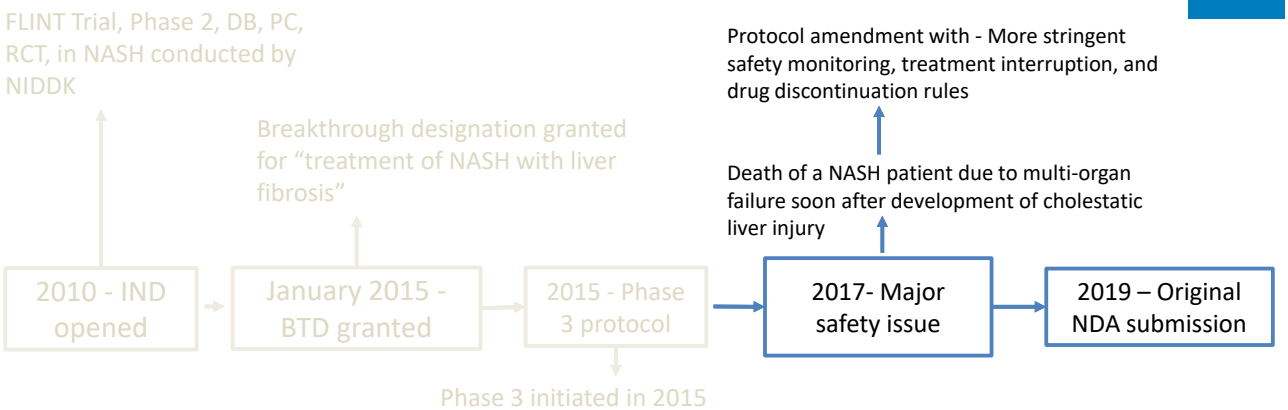
Regulatory History 2016 - 2019



NDA, New Drug Application

www.fda.gov

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June 2020 - Complete Response (CR) Issued: Efficacy

- OCA 25 mg met one of the surrogate endpoints
  - One stage reduction in fibrosis AND no worsening of NASH, treatment difference of 11.1% (95% CI: 5.3%, 17.0%)
- OCA 25 mg failed to meet the second surrogate endpoint
  - NASH resolution AND no worsening of fibrosis
- OCA 10 mg failed to meet either surrogate endpoint

June 2020 - Complete Response (CR) Issued: Safety Concerns

- Serious drug-induced liver injury (DILI) events
- Cholelithiasis and related complications
- Worsening of glycemic control, requiring addition of anti-diabetic drugs earlier
- Worsening of LDL cholesterol requiring initiation or intensification of statins
- Pruritus requiring symptomatic treatment or OCA discontinuation

Regulatory History: 2020 - 2022

- In the CR letter, FDA encouraged the Applicant to complete the clinical benefit outcomes trial before resubmitting the NDA
- FDA remained open to reviewing the current resubmission in the spirit of Breakthrough Designation (BTD) and unmet medical need
- FDA recommended reanalysis of histopathology due to the high rate of pathologists' discordance in the original submission
- Data we are considering in the resubmission include reanalysis of histopathology from subjects in the original submission plus new histopathology data from additional subjects

Agency's Concerns for AC Consideration

- Modest efficacy of OCA 25 mg on a histologic surrogate endpoint for treatment of NASH with Stage 2 or 3 fibrosis
- Safety of long-term use:
  - Serious cholestatic Drug-Induced Liver Injury (DILI) signal identified throughout the Applicant's OCA development program
    - Identified cases associated with long latency
    - Concerns about feasibility/adequacy of detecting DILI in timely manner to mitigate this risk
  - Management of multiple OCA-mediated off target effects (pruritus, LDL-C, and hyperglycemia)

Agency's Concerns for AC Consideration (cont'd)

- Uncertainty with identifying appropriate NASH patients:
  - NASH patients with Stage 2 or 3 fibrosis eligible for OCA treatment
  - Identify patients to discontinue OCA because they have progressed to cirrhosis:
    - OCA 25 mg failed to meet its primary endpoint of one stage reduction of fibrosis in subjects with cirrhosis due to NASH, Applicant conducted this as a separate trial*
    - Non-invasive tests (NITs) lack accuracy in distinguishing Stage 3 fibrosis from Stage 4 fibrosis (cirrhosis)
    - Unfavorable benefit-risk in patients with cirrhosis
- The benefit-risk of OCA 25 mg remains a concern for the proposed indication despite the new information submitted

 *https://ir.interceptpharma.com/news-releases/news-release-details/intercept-pharmaceuticals-announces-reverse-phase-3-study

Topics for Discussion

1. Discuss the strength of the available efficacy data on the histopathologic endpoint, a surrogate endpoint that is reasonably likely to predict clinical benefit, in NASH patients with Stage 2 or 3 fibrosis treated with OCA 25 mg.

Topics for Discussion

2. Based on the data presented concerning cholestatic drug-induced liver injury (DILI) in OCA 25 mg-treated patients, discuss:
   - Whether periodic liver enzyme monitoring could adequately mitigate the risk of DILI,
   - The frequency of such monitoring,
   - What stopping criteria should be developed to aid clinicians' decisions to discontinue treatment.

Voting Question

1. VOTE: (Yes/No/Abstain)

Given the available efficacy and safety data, do the benefits of OCA 25 mg outweigh the risks in NASH patients with Stage 2 or 3 fibrosis?

- Provide the rationale for your vote

Voting Question

2. Vote (Select either (A) or (B)/ Abstain)

Clinical outcome events in patients enrolled in Trial 747-303 will continue to be captured to evaluate clinical benefit in support of a future application for traditional approval. At present, which of the following would you recommend:

(A) Approval of OCA 25 mg at this time, under the accelerated (approval) pathway, based on efficacy data on a histopathologic surrogate and available clinical safety data;

OR

(B) Defer approval until clinical outcome data from Trial 747-303 are submitted and reviewed at which time the traditional approval pathway could be considered?

- Provide the rationale for your vote

U.S. FOOD & DRUG ADMINISTRATION

Regulatory Framework, Study Design, and Efficacy

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Outline

- Regulatory Framework
- Study 747-303
  - Overview
  - Subject Disposition and Baseline Histology Characteristics
  - Interim Analysis Efficacy Results

REGULATORY FRAMEWORK

Benefit-Risk Assessment

For a new drug to be approved for marketing in the United States

- FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling
- The demonstration of effectiveness requires substantial evidence that the drug will have the effect it purports or is represented to have
- The demonstration of safety requires a showing that **the benefits of the drug outweigh its risks**

Sources: Section 505(d) of the Food, Drug, and Cosmetic Act; Benefit-Risk Assessment for New Drug and Biological Products | FDA

Types of Outcomes and Endpoints

- **Clinical outcome***:* An outcome that describes or reflects how an individual *feels, functions, or survives*.
  - **Clinical benefit**: A positive therapeutic effect on a clinical outcome that is clinically meaningful

Sources: Accelerated Approval | FDA; Expedited Programs for Serious Conditions—Drugs and Biologics | FDA; BEST (Biomarkers, EndpointS, and other Tools) Resource - NCBI Bookshelf (nih.gov)

Types of Outcomes and Endpoints

- **Clinical outcome***:* An outcome that describes or reflects how an individual *feels, functions, or survives*.
  - **Clinical benefit**: A positive therapeutic effect on a clinical outcome that is clinically meaningful
- **Surrogate endpoint***:* a marker (such as a laboratory measurement, radiographic image, physical sign, or other measure) that is thought to predict clinical benefit, but is not itself a measure of clinical benefit
  - A **validated surrogate endpoint** has been shown to predict a specific clinical benefit. It can be used to support Traditional Approval.
  - A **surrogate endpoint that is reasonably likely to predict clinical benefit** has not reached the level of evidence needed to validate it. It can be used to support Accelerated Approval.

Sources: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Accelerated Approval | FDA; Expedited Programs for Serious Conditions—Drugs and Biologics | FDA; BEST (Biomarkers, EndpointS, and other Tools) Resource - NCBI Bookshelf (nih.gov)

Surrogate Endpoints for Non-Cirrhotic NASH

- Currently no validated surrogate endpoints
- Reasonably likely surrogate endpoints* were determined based on literature
- No currently approved drugs for NASH
- We do not have data from interventional trials that can be used to understand the quantitative relationship between treatment-induced changes in a surrogate endpoint and changes in clinical outcomes

*FDA, 2018, Guidance for Industry; Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment | FDA

Approval Pathways

Traditional

- Based on (a) measurement of clinical benefit or (b) effect on a surrogate endpoint known to predict clinical benefit (i.e., "validated")
- Authority: Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA); FDA Regulations

Accelerated

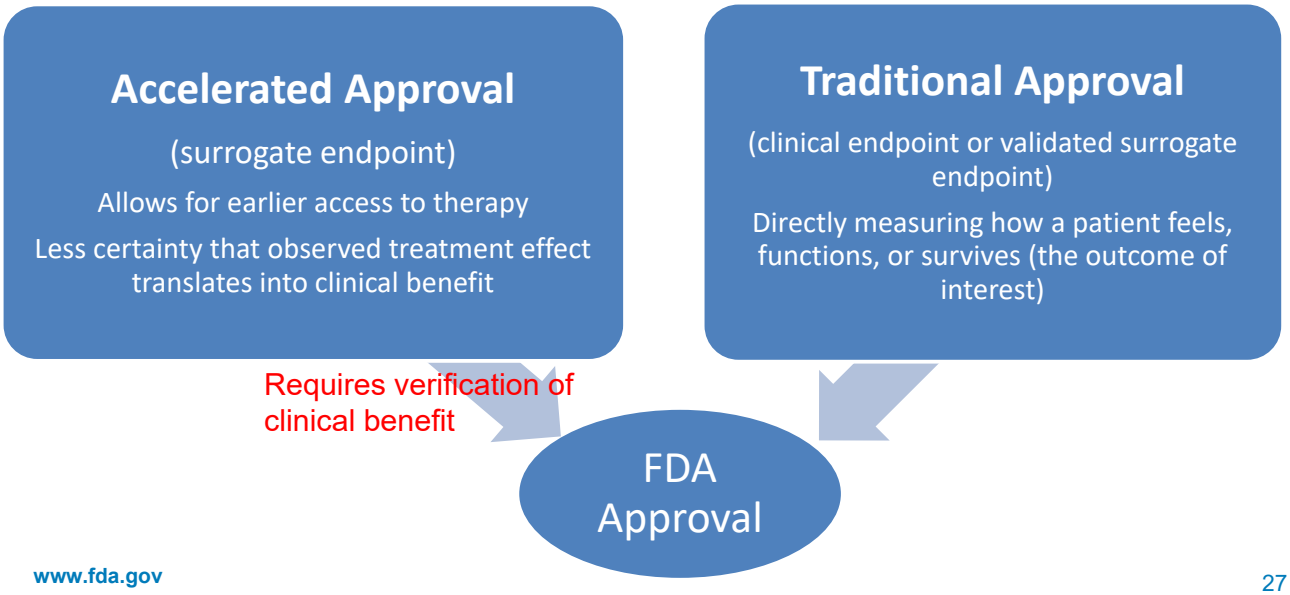
- Based on drug's effect on a surrogate or intermediate clinical endpoint "reasonably likely . . . to predict [a drug's] clinical benefit"
- Sponsor to conduct a confirmatory trial to verify clinical benefit
- Authority: FDCA section 506; FDA Regulations (21 CFR Part 314, Subpart H)
- Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval (FDCA section 505)

Accelerated Approval

- Can provide patients with serious and life-threatening diseases access to new therapies sooner for conditions for which there is unmet need for treatment
- Based on an effect on a surrogate or intermediate clinical endpoint that is *reasonably likely* to predict clinical benefit
- Accepts some additional **uncertainty** to provide earlier access
- After accelerated approval, FDA has required post-approval studies to "**verify and describe [the drug's] clinical benefit**"

 Sources: Accelerated Approval | FDA; Expedited Programs for Serious Conditions—Drugs and Biologics | FDA

Summary of Approval Pathways



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OVERVIEW OF STUDY 747-303

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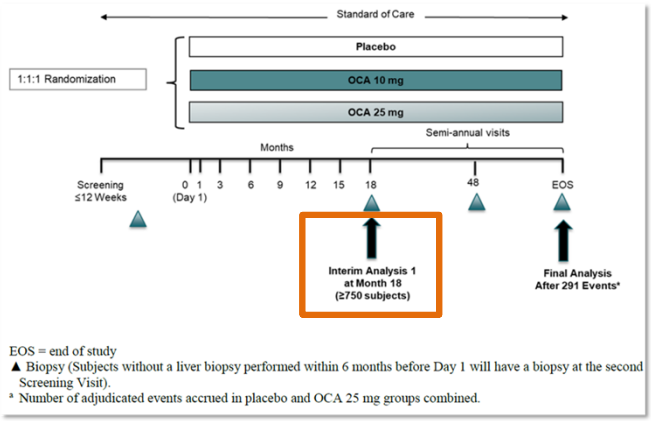
Design of Study 747-303

- Primary basis of efficacy and safety evaluation
- Ongoing, randomized, double-blind, placebo-controlled, multicenter
- Enrolled adult subjects with definite NASH
- 1:1:1 randomization OCA 25 mg, OCA 10 mg, or matching placebo orally once daily until end of study
- Efficacy evaluated in subjects with fibrosis stage 2 or stage 3 as defined by the NASH Clinical Research Network (CRN) scoring
- Assessments at baseline, Month 1, Month 3, then every 3 months until Month 18, then every 6 months

Design of Study 747-303

- Liver biopsies at Month 18, Month 48, and end of treatment under protocol Version 8 (08 Jan 2019) and earlier
- Month 18 interim analysis (N=931) of histological endpoints intended to support accelerated approval
- Study is still ongoing to evaluate clinical outcomes to support a traditional approval
- Endpoints evaluating clinical benefit remain blinded to maintain trial integrity



Source: Figure 1 of Applicant's Protocol 747-303 Version 8.0 (January 8, 2019)

NASH CRN Scoring System for Histological Assessment

NAFLD Activity Score (NAS)		Fibrosis Staging	
Parameter	Scoring Criteria	Parameter	Staging Criteria
Steatosis	0 = <5% 1 = 5% - 33% 2 = >33% - 66% 3 = >66%	Stage 0	No Fibrosis
Lobular Inflammation	0 = No Foci 1 = <2 Foci per 200 × field 2 = 2-4 Foci per 200 × field 3 = > 4 Foci per 200 × field	Stage 1 Stage 1a Stage 1b Stage 1c	Perisinusoidal or Periportal Mild, zone 3, persinusoidal Moderate, zone 3, perisinusoidal Portal / periportal
Ballooning	0 = None 1 = Few balloon cells 2 = Many cells / prominent ballooning	Stage 2	Perisinusoidal and portal / periportal
		Stage 3	Bridging fibrosis
		Stage 4	Cirrhosis

Source: Applicant's Table 7 on page 91 of protocol 747-303 (Version 9.0: July 29, 2019); Total NAS score is the sum of scores for steatosis, lobular inflammation, and ballooning.

Enrollment criteria: total NAS ≥ 4 with at least one point each in steatosis, lobular inflammation, and ballooning; and fibrosis stage 2 or 3 (higher-risk fibrosis stage 1a or 1b enrolled for safety cohort)

Month 18 Interim Analysis Primary Endpoints

Evaluated in subjects with fibrosis stage 2 or stage 3 at baseline:

- **Improvement of fibrosis** by ≥1 stage AND **no worsening of NASH** (no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis).
- **Resolution of NASH** by global interpretation and NAS of 0 for ballooning, 0-1 for inflammation AND **no worsening of fibrosis**.

These endpoints are considered by the Agency to be *surrogate endpoints that are reasonably likely to predict clinical benefit*

 Source: Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment | FDA

Final Analysis Primary Endpoints (not available in this submission)

The primary composite clinical endpoint that will be evaluated at the end of the trial is measured as the time to first occurrence of any of the following adjudicated events:

- Death (all cause)
- Model of end-stage liver disease (MELD) score ≥15
- Liver transplant
- Hospitalization (as defined by a stay of ≥24 hours) for onset of:
  - Variceal bleed
  - Hepatic encephalopathy (HE; as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Ascites secondary to cirrhosis and requiring medical intervention (e.g., diuretics or paracentesis)
- Histological progression to cirrhosis

Study 747-303 is fully enrolled and ongoing to evaluate these outcomes, and results for this endpoint remain blinded to maintain the integrity of the ongoing trial

Efficacy Analysis

- Applicant prespecified a testing strategy to control the overall type I error rate when conducting multiple hypothesis tests for:
  - Month 18 interim analysis and final analysis
  - OCA 25 mg vs. placebo and OCA 10 mg vs. placebo
  - Two primary endpoints for Month 18 interim analysis
- Two primary endpoints are not coprimary
  - Statistical significance on either endpoint was considered acceptable to support accelerated approval
- P-values should not be compared to standard 0.05 threshold and 95% confidence intervals (CIs) cannot be used to determine statistical significance

Liver Biopsy Read Methods

- Different methods for scoring biopsy slides
  - Original NDA review focused on a **central method**, in which a single pathologist's scores are used for each subject's efficacy assessment
  - NDA resubmission review focused on a **consensus method**, in which at least two of three pathologists need to agree on score
- Consensus method was used to address previous FDA concerns about poor to moderate inter- and intra-reader concordance in the histopathology scores using the central method

Analysis Populations for Study 747-303

- **Safety analysis population (N=2477):** all randomized and treated subjects up to data cutoff (December 31, 2021)
- **ITT_old (N=931):** all fibrosis stages 2 or 3 subjects (central method) who were randomized by July 15, 2017 and received at least one dose of investigational product (IP)
  - Pre-specified primary efficacy analysis population for Month 18 interim analysis
  - Focus of efficacy evaluation for the original NDA submission
- **ITT_histology (N=1607):** all fibrosis stages 2 or 3 subjects (central method) who were randomized, received at least one dose of IP, and who had or were expected to have completed a Month 18 biopsy per protocol Version 8 or earlier
  - An additional efficacy evaluation considered during the NDA resubmission

Discussion of Statistical Results

- Statistical significance can only be discussed for the prespecified Month 18 interim analysis of the **ITT_old** analysis population
- Analyses of **ITT_histology**
  - Separate interim analysis that was not prespecified and not accounted for in the method to control the overall type I error rate
  - P-values and discussion of statistical significance are not applicable
  - Larger sample size provides additional precision in the estimation of the treatment effect

STUDY 747-303 SUBJECT DISPOSITION AND BASELINE HISTOLOGY CHARACTERISTICS

Subject Disposition

All Subjects Randomized and Treated With at Least One Dose by December 31, 2021

Disposition	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)	Placebo N=825 n (%)
Randomized	825	829	826
ITT_old	312	308	311
ITT_histology	532	539	536
Safety population	825	827	825
Discontinued study drug	277 (33.7)	335 (40.5)	267 (32.2)
Adverse event	103 (12.5)	185 (22.4)	99 (12)
Lost to follow-up	23 (2.8)	20 (2.4)	33 (4)
Noncompliance with study drug	3 (0.4)	4 (0.5)	0 (0)
Physician decision	12 (1.5)	13 (1.6)	9 (1.1)
Protocol violation	3 (0.4)	1 (0.1)	3 (0.4)
Site terminated by sponsor	8 (1)	2 (0.2)	1 (0.1)
Withdrawal by subject	78 (9.5)	72 (8.7)	77 (9.3)
Death	2 (0.2)	2 (0.2)	2 (0.2)
Pregnancy	0 (0)	0 (0)	2 (0.2)
COVID-19 non-AE related issues	1 (0.1)	0 (0)	1 (0.1)
Other	44 (5.3)	36 (4.4)	40 (4.8)

Source: Clinical data scientist's analysis of adae.xpt; Software: R (Ver 4.1.0)
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; COVID-19, coronavirus disease 2019; ITT, intent-to-treat; OCA, obeticholic acid

Baseline Histology Characteristics

ITT_histology

	OCA 10 mg N=532 n (%)	OCA 25 mg N=539 n (%)	Placebo N=536 n (%)
Baseline fibrosis stage (central method)			
Stage 2	219 (41)	238 (44)	223 (42)
Stage 3	313 (59)	301 (56)	313 (58)
Baseline fibrosis stage (consensus method)			
Stage 0	0	1 (<1)	1 (<1)
Stage 1	17 (3)	17 (3)	23 (4)
Stage 2	135 (25)	142 (26)	136 (25)
Stage 3	223 (42)	216 (40)	227 (42)
Stage 4 (cirrhosis)	69 (13)	66 (12)	70 (13)
Not evaluable	9 (2)	3 (<1)	5 (1)
Missing	79 (15)	94 (17)	74 (14)

Source: Statistical reviewer's analysis of adsl.xpt.
Abbreviations: OCA, obeticholic acid; N, number of subjects in treatment group; n, number of subjects with given characteristic

STUDY 747-303 INTERIM ANALYSIS EFFICACY RESULTS

Efficacy Overview: Month 18 Interim Analysis

- OCA 25 mg demonstrated superiority to placebo on one of two primary endpoints
- OCA 10 mg failed to demonstrate superiority to placebo on either of the two primary endpoints
- The overall conclusions regarding the treatment effect are generally consistent between the central method in the original NDA submission and the consensus method in the NDA resubmission
- Month 18 primary endpoints are reasonably likely surrogate endpoints
  - There is uncertainty about how the magnitude of changes observed on the surrogate endpoints may translate to meaningful changes in clinical outcomes

MONTH 18 PRIMARY ENDPOINT RESULTS
IMPROVEMENT OF FIBROSIS AND NO WORSENING OF NASH

Month 18 Primary Endpoint Results
Improvement of Fibrosis and No Worsening of NASH

	OCA 10 mg n (%)	OCA 25 mg n (%)	Placebo n (%)
ITT_old	**N=312**	**N=308**	**N=311**
Central method	55 (17.6)	71 (23.1)	37 (11.9)
Consensus method	44 (14.1)	69 (22.4)	30 (9.6)

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results.

Month 18 Primary Endpoint Results
Improvement of Fibrosis and No Worsening of NASH

	OCA 10 mg n (%)	OCA 25 mg n (%)	Placebo n (%)	Risk Difference 10 mg-Placebo (95% CI)	Risk Difference 25 mg-Placebo (95% CI)
ITT_old	**N=312**	**N=308**	**N=311**		
Central method	55 (17.6)	71 (23.1)	37 (11.9)	5.7 (0.2, 11.3)	11.1 (5.3, 17.0)*
Consensus method	44 (14.1)	69 (22.4)	30 (9.6)	4.5 (-0.6, 9.5)	12.8 (7.0, 18.5)*

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. Statistical significance based on CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
* denotes statistical significance.
Note: 95% confidence intervals cannot be used to determine statistical significance.

- OCA 25 mg arm demonstrated superiority to placebo
- OCA 10 mg arm failed to demonstrate superiority to placebo

Month 18 Primary Endpoint Results
Improvement of Fibrosis and No Worsening of NASH

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ITT_histology					
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ITT _histology	**N=532**	**N=539**	**N=536**		
Consensus method	86 (16.2)	113 (21.0)	66 (12.3)		

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. Statistical significance based on CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
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* denotes statistical significance.
Note: 95% confidence intervals cannot be used to determine statistical significance.

- The estimated risk difference (95% CI) comparing OCA 25 mg to placebo ranged from 8.6% (4.2%, 13.0%) to 12.8% (7.0%, 18.5%) across the different analysis populations and histopathology read methods

MONTH 18 PRIMARY ENDPOINT RESULTS
RESOLUTION OF NASH AND NO WORSENING OF FIBROSIS

Month 18 Primary Endpoint Results
Resolution of NASH and No Worsening of Fibrosis

	OCA 10 mg n (%)	OCA 25 mg n (%)	Placebo n (%)	Risk Difference 10 mg-Placebo (95% CI)	Risk Difference 25 mg-Placebo (95% CI)
ITT_old	**N=312**	**N=308**	**N=311**		
Central method	35 (11.2)	36 (11.7)	25 (8.0)	3.1 (-1.4, 7.7)	3.6 (-1.0, 8.3)
Consensus method	19 (6.1)	20 (6.5)	11 (3.5)	2.5 (-0.8, 5.9)	3.0 (-0.5, 6.4)
ITT _histology	**N=532**	**N=539**	**N=536**		
Consensus method	34 (6.4)	39 (7.2)	19 (3.5)	2.8 (0.2, 5.4)	3.7 (1.0, 6.4)

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. Statistical significance based on CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
Note: 95% confidence intervals cannot be used to determine statistical significance.

- Both dose groups failed to demonstrate superiority to placebo on this Month 18 primary endpoint

Summary of Efficacy

- OCA 25 mg demonstrated superiority to placebo on one of the two Month 18 primary endpoints, "improvement of fibrosis and no worsening of NASH"
  - Estimated risk difference (95% CI) ranged from 8.6% (4.2%, 13.0%) to 12.8% (7.0%, 18.5%) across different analyses
- OCA 25 mg failed to demonstrate superiority to placebo on "resolution of NASH and no worsening of fibrosis"
- OCA 10 mg failed to demonstrate superiority to placebo on either of the two Month 18 primary endpoints
- There is uncertainty how the magnitude of change on a surrogate endpoint may translate to meaningful changes in clinical outcomes

U.S. FOOD & DRUG ADMINISTRATION

Drug-Induced Liver Injury Assessment

Paul H. Hayashi, MD, MPH, FAASLD
DILI Team Leader
Division of Hepatology and Nutrition
Office of New Drugs
CDER, FDA

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Drug-Induced Liver Injury (DILI) Due to OCA

- DILI fatality rate
- Other cholestatic OCA related DILI cases in 747-303
- Risk mitigation challenges

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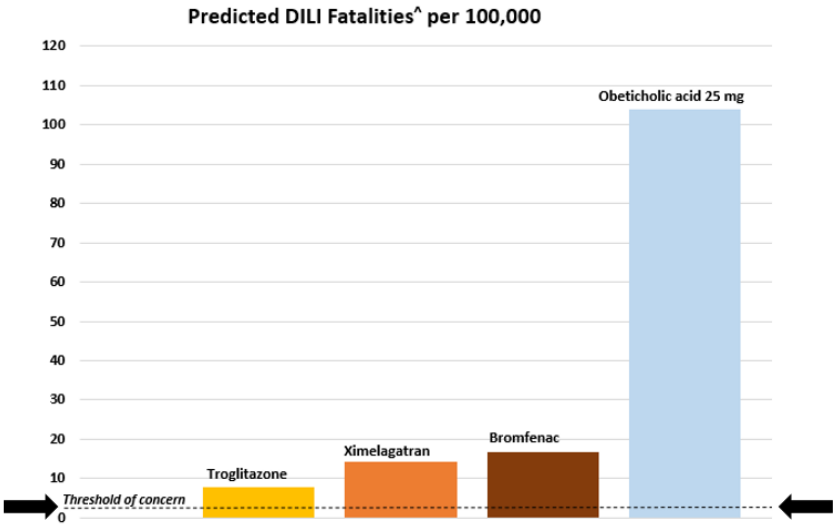
DILI Fatality Rates and Historical Context



^Fatality = death or liver transplant due to DILI

*FDA Guidance for Industry Drug-Induced Liver Injury: Premarket Clinical Evaluation 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

www.fda.gov

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Subject #3 (Study 747-303)

63-year-old man with NASH and stage 2 fibrosis.

No history of gallstone disease.

Day 1: OCA 25 mg/d

Day 129: vomiting, pruritus->rash, dark urine, diarrhea

Day 142: Self-discontinues OCA

Day 150: Bilirubin 26 mg/dL, ALP 399, ALT 139

Liver bx: DILI versus bile duct obstruction

CT, MRI & US: Normal bile ducts; small dependent stone in GB

Rash: "pruritus/prurigo nodules…thought secondary to methicillin-sensitive Staphylococcal aureus bacteremia."

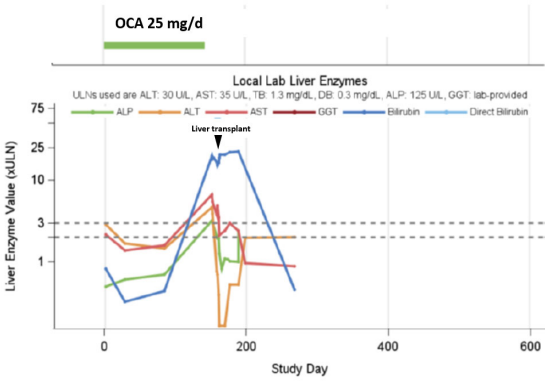
Blood tests: No etiology found

Listed for liver transplant with portal hypertension, jaundice and hepatic encephalopathy

Day 164: "S. aureus bacteremia was…resolved. Blood cultures negative."

Day 175: Discharged to home; MELD 31

Day 187: Admitted and had liver transplant; MELD 39; "standard piggyback caval anastomosis"



Source: Table generated by FDA DILI Team; Data from Applicant's response to information Request, HSAC Case Packets, Jan 24, 2023

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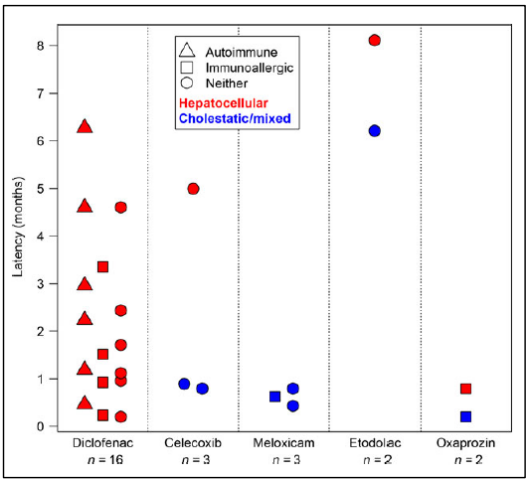
Diclofenac Hepatotoxicity

- Schmeltzer PA, et al., for the Drug-Induced Liver Injury Network (DILIN). Liver injury from nonsteroidal anti-inflammatory drugs in the United States.*
- LiverTox®
  - "The majority of cases present within 2 to 6 months, and the more severe cases tend to present earlier. The pattern of injury is almost exclusively hepatocellular, although cases presenting with mixed patterns have been reported."**



* *Liver International*. 2015; 36:603-9.
**https://www.ncbi.nlm.nih.gov/books/NBK547953/

www.fda.gov

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OCA Hepatotoxicity

- Eaton JE, et al. Liver Injury in Patients with Cholestatic Liver Disease Treated with Obeticholic Acid.*
  - Case series of eight PBC or PSC patients with OCA hepatotoxicity
  - **Mean Latency = 210 days +/- 104**
  - **Pattern of Injury: cholestatic in all eight**
  - Four had acute-on-chronic liver failure requiring transplant.
- May 26, 2021: "Due to risk of serious liver injury, FDA restricts use of Ocaliva (obeticholic acid) in primary biliary cholangitis (PBC) patient with advanced cirrhosis"**

**Hepatology*. 2020; 71:1511-1514
** https://www.fda.gov/drugs/drug-safety-and-availability/due-risk-serious-liver-injury-fda-restricts-use-ocaliva-obeticholic-acid-primary-biliary-cholangitis

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Subject #3 (Study 747-303)

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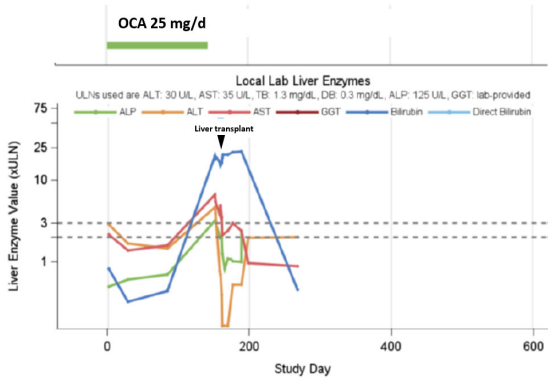

Source: Table generated by FDA DILI Team; Data from Applicant's response to information Request, HSAC Case Packets, Jan 24, 2023

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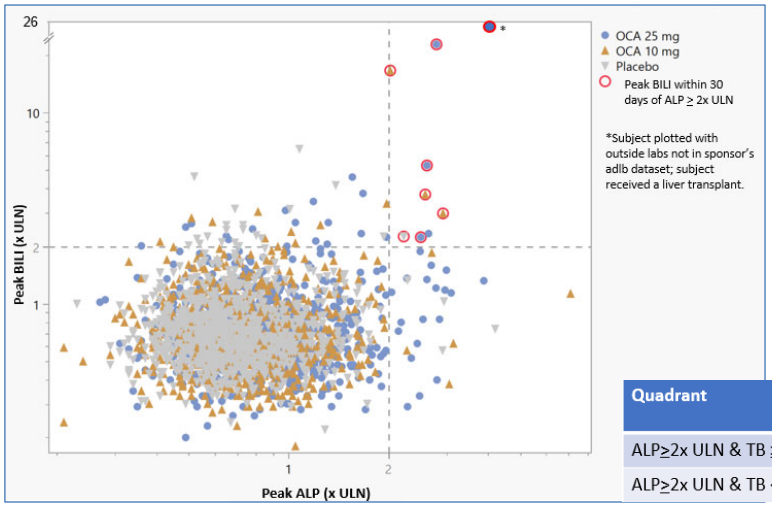
Cholestatic Scatter Plot – Study 747-303



Quadrant	OCA 25 mg (N = 827)	Placebo (N = 825)	Risk Difference for OCA 25 mg over Placebo (95% CI)
ALP≥2x ULN & TB ≥2x ULN	5 (0.6%)	1 (0.1%)	0.24 (-0.23, 0.72)
ALP≥2x ULN & TB <2x ULN	20 (2.4%)	4 (0.5%)	1.93 (0.78, 3.08)

Graph generated by FDA DILI Team using JMP Clinical 8.0; data from adlb and adsl datasets

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Blinded Hepatology Safety Adjudication Committee (HSAC) Assessments of Liver Injury Events in Study 747-303

Blinded HSAC assessment	Study Arm: 25 mg	% Within Arm	PBO	% Within Arm	
Highly likely	1	*0.5*	0	*0*	
Probable	7	*3.5*	1	*0.6*	
Possible	57	*28.6*	11	*6.8*	
Unlikely	134	*67.3*	150	*92.6*	
Totals	199	*100*	162	*100*	361

Source: Table generated by FDA DILI Team; Data from Applicant's response to information request, HSAC Case Packets, Jan 24, 2023

Moderate to Severe Liver Injury Cases—747-303

Assessed as at least possible DILI by FDA or HSAC

#	OCA dose (mg/d)	Unblind FDA Score*	Blinded HSAC Score*	Alternate diagnosis	Fibrosis at baseline	Age (yr)	Fatality	Days OCA start to injury onset	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak	Notes
1	25	3 ←	4	Not applicable	F2	63	Yes	150	139	233	399	28.9	1.1	Liver transplant Day 187
2	10	3	3	Not applicable	F3	49	No	28	135	168	304	19.9	1.4	
3	25	3	3	Not applicable	F3	63	No	28	50	100	234	5.2	0.7	
4	25	3 or 4 ←	5	Gallstone disease progression	F3	60	Yes	530	57	108	294	37.4	0.6	ACLF; new porcelain GB
5	10	4	4	De novo gallstone disease	F1b	70	No	912	399	375	104	11.7	11.7	ERCP pancreatitis
6	25	4	4	Fracture; cephalosporin liver injury	F2	68	No	408	90	116	529	3.6	0.5	
7	25	4	4	De novo gallstone disease; other DILI	F3	65	No	461	108	80	218	11.9	1.5	ERCP x 3
8	10	4	4	Gallstone disease	F2	59	No	833	62	93	407	2.2	0.5	
9	25	4	→ 3	Unknown	F3	57	No	28	196	130	297	2.7	2.0	
10	25	4	4	Disease progression	F3	64	No	176	38	84	249	2.8	0.5	
11	25	5	→ 4	Unknown	F2	59	No	363	150	66	197	0.9	2.3	
12	25	5	→ 4	AM/CL liver injury	F3	68	No	251	100	119	393	6.4	0.8	
					Mean	***62***		***347***	***127***	***139***	***302***	***11.1***	***2.0***	
					Std dev	*5.5*		*287*	*94*	*83*	*110*	*11.3*	*3.0*	
					Median	***63***		***307***	***104***	***112***	***296***	***5.8***	***0.9***	
					Min	*49*		*28*	*38*	*66*	*104*	*0.9*	*0.5*	
					Max	*70*		*912*	*399*	*375*	*529*	*37.4*	*11.7*	

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate DILI

R-value = (ALT/ULN) ÷ (AP/ULN); R ≥ 5: hepatocellular; R 2 to 5 mixed; R ≤ 2 cholestatic

Source: Table generated by FDA DILI Team; Data from Applicant's response to information request, HSAC Case Packets, Jan 24, 2023

Risk Mitigation Challenges

- DILI long latencies with wide range
  - Median 307 day (28-912 days)
- High frequency of liver enzyme and bilirubin checks
- Complex action plans for liver enzyme and bilirubin changes

Why the Latency May Be So Long: DILI and Dose Response

Blinded Hepatology Safety Adjudication Committee (HSAC) Assessments of Liver Injury Events
Study 747-303

Blinded HSAC assessment	10 mg	*% Within Arm*	25 mg	*% Within Arm*	PBO	*% Within Arm*	
Highly likely	0	*0*	1	*0.5*	0	*0*	
Probable	1	*0.6*	7	*3.5*	1	*0.6*	
Possible	24	*13.6*	57	*28.6*	11	*6.8*	
Unlikely	151	*85.8*	134	*67.3*	150	*92.6*	
	176	*100*	199	*100*	162	*100*	537

Source: Table generated by FDA DILI Team; Data from Applicant's response to information request, HSAC Case Packets, Jan 24, 2023

Possible Mechanism for OCA-Associated Gallstone Formation

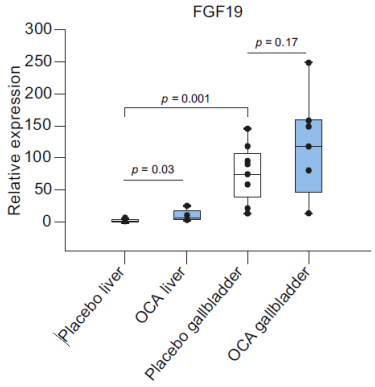
Al-Dury S, et al. Obeticholic acid may increase the risk of gallstone formation in susceptible patients.*

Methods

- Randomized, double-blind, placebo controlled
  - 20 patients awaiting elective cholecystectomy
  - OCA 25 mg/d versus placebo (PBO) x three weeks
- Bile acids, liver biopsy, serum and gallbladder assessed

Major Findings

- Increased cholesterol saturation index
  - **OCA**, **2.8** ± 1.1; **PBO 1.9** ± 0.8, p<0.05
- Increased FGF-19§ expression



Journal of Hepatology. 2019; 71:986-991
§ FGF, fibroblast growth factor

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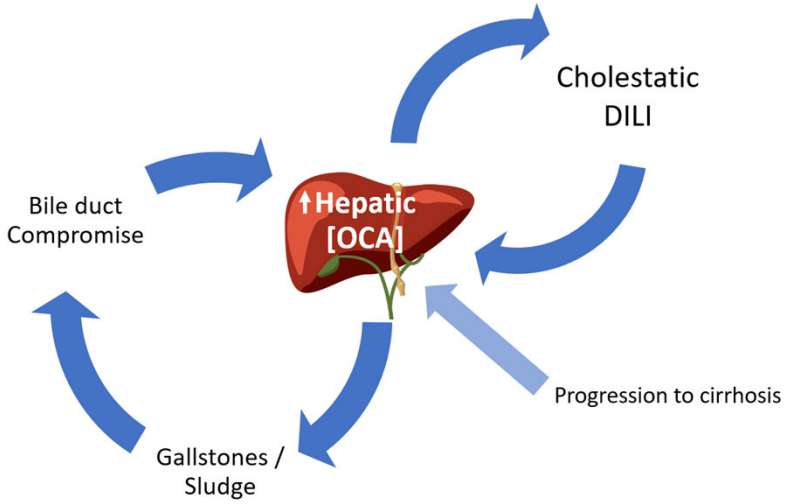
Why the Latency May Be So Long: Interaction of OCA Mechanisms of Liver Injury



Source: Figure generated by FDA DILI Team

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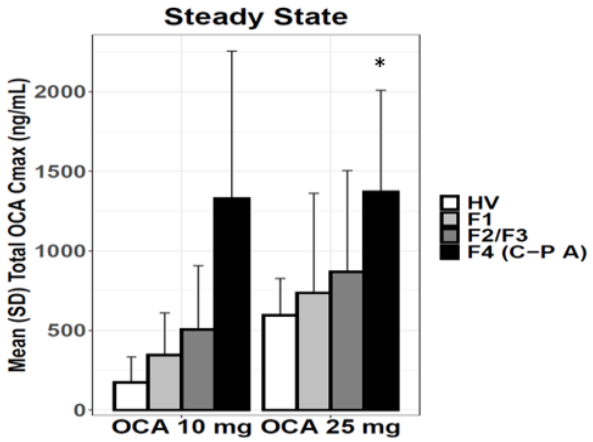
Subject 1 and Total OCA Plasma C_{max} in NASH Patients by Dose and Fibrosis Stage

Subject 1:

- F3 at baseline; no gallstone history
- Day 1: OCA 25 mg/d
- Day 444: uneventful lap chole for new gallstones
- Day 461: jaundice; OCA stopped; ERCP*-- No leak; sludge removed; stent placed
- Day 465: Bilirubin continues to rise; 2nd ERCP normal
- **Plasma Total OCA = 3950 ng/ml**

(4 days after OCA stop and first ERCP)



- C_{max} around 9-10 hours post-dose
- Highest observed C_{max} in NASH with F4 at OCA 25 mg = 2180 ng/ml

* endoscopic retrograde cholangiopancreatography

Source: Graph generated by Clinical Pharmacology Team using data from Studies 747-117 & 747-118

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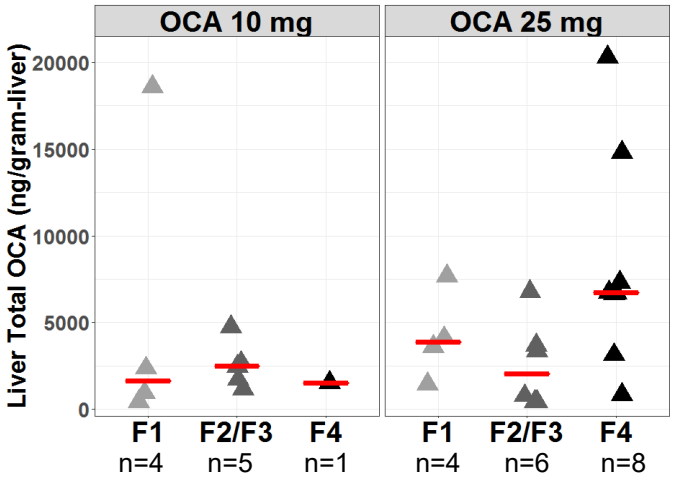
Total OCA Concentrations in the Liver at Steady State in NASH Patients by Fibrosis Stage



- Exposure of total OCA was higher in liver (>10-fold) relative to plasma trough concentrations
- Increasing trend with dose
- Within each dosing group, the total OCA exposure in the liver appears to be similar across fibrosis stages F1 to F3.
- **Limitations:**
  - Large variability in concentrations
  - Small sample size

F1 – F3: data from 747-117; F4 (C-P A): combined data from 747-117 and 747-118

Source: Clinical Pharmacology Team generated graph using data from Studies 747-117 & 747-118

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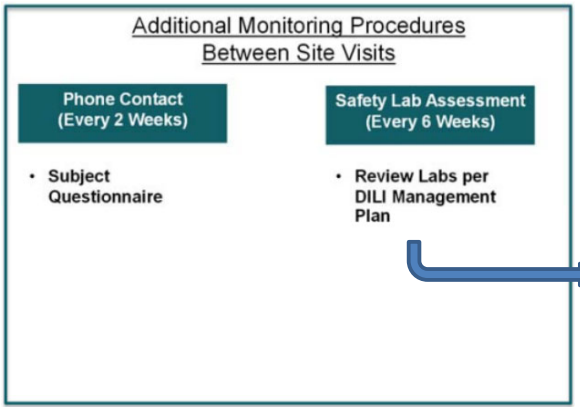
Pace of DILI Onset and Frequency of Surveillance

#	Unblind DHN Score*	Blinded HSAC Score*	Days OCA start to injury onset	Days between last prior liver tests and DILI onset	Bilirubin onset (mg/dL)	Bilirubin peak (mg/dL)
1	3 or 4	5	530	60	7.67	37.4
2	3	4	150	67	25.7	28.9
3	3	3	28	28	11.1	19.9
4	4	4	461	36	6.5	11.9
5	4	4	912	67	2.8	11.7

Source: Table generated by FDA DILI Team; Data from Applicant's response to information request, HSAC Case Packets, Jan 24, 2023

Study 747-303: Amendment Sept 19, 2017



Criteria Resulting in Repeat Testing		
Baseline	**Upper Laboratory Threshold**	**Frequency of Monitoring (Repeat Testing)**
Key Liver Parameters for Hepatic Injury		
ALT ≤ULN	≥3x ULN	2-3 days
ALT >ULN and <2x ULN	≥3x baseline or incremental increase from baseline >250 U/L	2-3 days
ALT ≥ 2x ULN	≥2x baseline or incremental increase from baseline >250 U/L	
AST ≤ULN	≥3x ULN	2-3 days
AST >ULN and <2x ULN	≥3x baseline or incremental increase from baseline >250 U/L	2-3 days
AST ≥ 2x ULN	≥2x baseline or incremental increase from baseline >250 U/L	
ALP ≤ULN	≥1.5x ULN	7 days
ALP >ULN	≥1.5x baseline	7 days
Total bilirubin ≤ULN[a]	≥1.5x baseline AND >ULN	2-3 days
Total bilirubin >ULN[a]	≥1.5x baseline	2-3 days

Source: Clinical Study Report 747-303 IA, 16.1.1 Protocol and Protocol Amendments, Safety Amendment, Sep 19, 2017

Moderate to Severe Liver Injury Cases—747-303

Assessed as at Least Possible DILI by FDA or HSAC

#	OCA dose (mg/d)	Unblind FDA Score*	Blinded HSAC Score*	Alternate diagnosis	Fibrosis at baseliine	Age (yr)	Fatality	Days OCA start to injury	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak	Notes	DILI onset date if after 10/1/17
1	25	3 ←	4	Not applicable	F2	63	Yes	150	139	233	399	28.9	1.1	Liver transplant Day 187	
2	**10**	**3**	**3**	**Not applicable**	**F3**	**49**	**No**	**28**	**135**	**168**	**304**	**19.9**	**1.4**		**12/17/2018**
3	25	3	3	Not applicable	F3	63	No	28	50	100	234	5.2	0.7		
4	**25**	**3 or 4 ←**	**5**	**Gallstone disease progression**	**F3**	**60**	**Yes**	**530**	**57**	**108**	**294**	**37.4**	**0.6**	**ACLF; new porcelain GB**	**8/20/2019**
5	**10**	**4**	**4**	**De novo gallstone disease**	**F1b**	**70**	**No**	**912**	**399**	**375**	**104**	**11.7**	**11.7**	**ERCP pancreatitis**	**12/15/2019**
6	**25**	**4**	**4**	**Fracture; cephalosporin liver injury**	**F2**	**68**	**No**	**408**	**90**	**116**	**529**	**3.6**	**0.5**		**3/20/2019**
7	**25**	**4**	**4**	**De novo gallstone disease; other DILI**	**F3**	**65**	**No**	**461**	**108**	**80**	**218**	**11.9**	**1.5**	**ERCP x 3**	**9/30/2018**
8	**10**	**4**	**4**	**Gallstone disease**	**F2**	**59**	**No**	**833**	**62**	**93**	**407**	**2.2**	**0.5**		**11/7/2018**
9	25	4 →	3	Unknown	F3	57	No	28	196	130	297	2.7	2.0		
10	25	4	4	Disease progression	F3	64	No	176	38	84	249	2.8	0.5		
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R-value = (ALT/ULN) ÷ (AP/ULN); R ≥ 5: hepatocellular; R 2 to 5 mixed; R ≤ 2 cholestatic

Source: Table generated by FDA DILI Team; Data from Applicant's response to information Request, HSAC Case Packets, Jan 24, 2023

Lessons from Troglitazone

2009 FDA Guidance for Drug-Induced Liver Injury

1) "monitoring recommendations may not be well followed by physicians, even after warning letters are sent to all practicing physicians; and
2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed."

*FDA Guidance for Industry Drug-Induced Liver Injury: Premarket Clinical Evaluation 2009.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Summary of OCA Associated DILI

- DILI fatality rate for OCA 25 mg is well-above that of drugs removed from the market, or not approved, because of fatal DILI
- Study 747-303 had other cholestatic DILI cases with severe jaundice
- Long surveillance periods will likely erode compliance with risk mitigation
- Frequent and multiple test monitoring followed by complex follow-up plans will also likely erode compliance

U.S. FOOD & DRUG ADMINISTRATION

Safety Assessment
(non-DILI)

Charmaine Stewart, MD, FAASLD, AGAF, FACP
Clinical Reviewer
Division of Hepatology and Nutrition
Office of New Drugs
CDER, FDA

May 19, 2023

Outline

- Safety database (Study 747-303)
- Population
- Adverse Events of Special Interest (AESI)

Safety Population, Study 747-303

- 1968 subjects from original submission + additional 509 subjects
- Safety population: 2477 subjects from Study 747-303 who received at least one dose of study drug
  - Randomized to OCA 25 mg (n=827), placebo (n=825), and OCA 10 mg (n=825)
  - 7886 total PY of exposure, compared to 2395 PY in the original submission
- Data presented compare the safety results of the proposed to-be-marketed dose (OCA 25 mg) to placebo

Risk Estimation

- Incident AE outcomes (i.e., first event) were estimated using incidence rates (IR) for within-arm estimates and incidence rate differences (IRD) for comparing OCA to Placebo
- Incidence rates (IR): Estimated as the number of incident AE outcomes (i.e., first event) per 100 person years (PY)
- The IRD is the difference between the IR in OCA and placebo
- Time at-risk
  - On-treatment analysis: Time from randomization to treatment discontinuation plus 30 days
  - On-study analysis: Time from randomization until trial discontinuation – includes events that occur while on treatment and off treatment

Risks and Outcome Definitions

- Cholelithiasis
  - Incidence of gallbladder disease and related complications
  - Incidence of cholecystectomy
- Dyslipidemia
  - Incidence of sustained LDL-C >= 15% over baseline
  - Initiation or increased dosage of statins
  - Mean changes of LDL-C over time
- Dysglycemia
  - Impact of study drug on glycemic control according to baseline characteristics i.e. normoglycemia, prediabetes, diabetes
- Pruritus
  - Incidence of pruritus (any grade) and severe pruritus
  - Impact on discontinuation of study drug

Cholelithiasis and Complications

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Cholelithiasis and Complications Were Associated With Higher Morbidity in the OCA 25 mg Arm Versus Placebo

Adverse Events of Special Interest	**OCA 25 mg N=827** n [IR per 100 PY]	**Placebo N=825** n [IR per 100 PY]	IR Difference (95% CI) per 100 PY
Gallbladder disease and related complications*	67 [2.5]	35 [1.2]	1.2 (0.5, 1.9)
Severe gallbladder disease and related complications**	23 [0.8]	7 [0.2]	0.6 (0.2, 0.9)
Cholecystectomy	38 [1.3]	17 [0.6]	0.8 (0.3, 1.3)

Source: FDA Statistical reviewer's analysis based on Applicant-submitted data, adtteir4.xpt.
On-Study analyses up to cutoff date.
*Applicant defined term: Gallbladder disease, biliary sepsis, ascending cholangitis, Gallbladder abscess, Gallbladder empyema, Cholangitis, Cholangitis acute, Cholangitis chronic, or Perforation bile duct.
**Applicant defined severity: AE grade severe (requires hospitalization), life-threatening, or death).

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Morbidity Risk of Cholelithiasis and Associated Complications May Be High

For every **1000** patients treated for one year with OCA 25 mg, we can expect approximately**:**

- **12** additional cases of gallbladder disease and related complications
- **6** additional cases of severe gallbladder disease and related complications
- **8** additional cholecystectomies

than would have been observed on placebo

These numbers would double if treated for **two** years

Dyslipidemia

Baseline Characteristics – LDL-C Related

(Study 747-303)

Baseline Parameters	OCA 25 MG N=827	Placebo N=825
Mean LDL-C (mg/dL)	114	116
LDL-C ≥130 mg/dL (%)	33%	36%
Lipid-lowering drugs (%)	52%	53%

Source: Applicant Submission, 17 February, 2023, SDN 110, Table 1, 23 February, 2023, SDN 112, Table 486.11.1

Sustained Elevations in LDL-C

(Study 747-303)

Adverse Events of Special Interest	OCA 25 mg N= 827 n [IR per 100 PY]	Placebo N=825 n [IR per 100 PY]	IR Difference (95% CI) per 100 PY
Sustained* LDL-C ≥ 15% over Baseline	488 [42.6]	204 [9.2]	33.4 (29.4, 37.4)

Source: FDA Clinical data scientist's analysis of adlb.xpt
Abbreviations: CI, confidence interval; [IR], incidence rate per 100 PY; IR Diff., incidence rate difference between OCA and placebo per 100 PY; LDL-C, low-density lipoprotein cholesterol; OCA, obeticholic acid; n, number of subjects who experienced at least one event; PY= Patient years of follow up until the earliest of: first event, treatment discontinuation + 30 days, study discontinuation, loss of follow-up, cut-off date, or death

On-treatment + 30 days
Sustained* defined as at least two consecutive elevations of 15% over baseline.

Statin Use

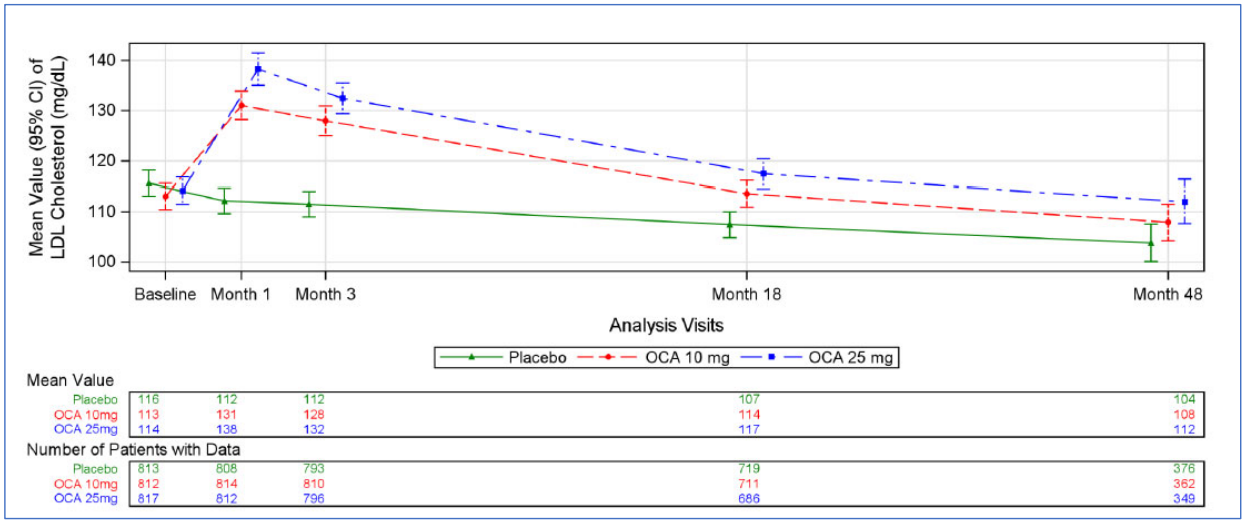
(Study 747-303)

	OCA 25 MG	Placebo
No Statin at Baseline	450	448
Initiated Statins	265 (59%)	142 (32%)
On Statin at Baseline	377	377
Intensified Statin	75 (20%)	45 (12%)

Applicant submission to Information Request, 24 February, 2023, SDN 114, Table 486.3.1

Mean LDL-C Over Time

(Study 747-303)



Study 747-303, Safety all population, on-study. Source: Response to FDA IR, submitted 24 February, 2023. SDN 114. Figure 486.7.1.1

LDL-C and OCA Treatment: Conclusions

- OCA treatment is associated with elevations in LDL-C and a higher proportion of OCA treated patients started lipid modifying therapy or required intensified statin therapy (e.g., higher doses, switch to rosuvastatin)
- Initiation of statins mitigated LDL-C elevations associated with OCA, but LDL-C values remained numerically higher compared to the placebo group despite statin treatment at month 18 and month 48

Dysglycemia

Dysglycemia

- Baseline characteristics similar between OCA 25 mg and placebo
  - ~16% normoglycemia
  - ~19% prediabetes
  - ~65% T2DM
- Inclusion Criteria: HbA1c < 9.5%
- Monitoring: FPG & HbA1c
  - month 1, q3 months for first 18 months, then q6 months
- Site investigators followed ADA guidelines for diabetes management
- FDA analyzed glycemic effects (FPG, HbA1c) by baseline status:
  - normoglycemia, prediabetes, T2DM

ADA: American Diabetes Association FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c

Conversion of Glycemic Status Observed

- Baseline normoglycemia: OCA 25 mg decreased the median time to incident prediabetes by approximately 9 months compared to placebo (3 months OCA vs. 12 months placebo)
  - At 36 months, 86% of OCA-treated subjects and 79% of placebo-treated subjects converted to prediabetes
- Baseline prediabetes: At 3 months, 21% OCA-treated subjects and 11% of placebo-treated subjects converted to diabetes
  - At 36 months, this imbalance persisted: 44% of OCA-treated subjects and 35% of placebo-treated subjects converted to diabetes

Loss of Glycemic Control

- Baseline Diabetics: OCA 25 mg decreased the median time to clinically significant loss of glycemic control* by ~ 2 months compared to placebo:
  - 4 months for placebo vs. 2 months for OCA
  - At 36 months, 88% OCA-treated subjects and 84% of placebo-treated subjects experienced loss of glycemic control

*loss of glycemic control, defined as
(1) increase in dose or initiation of new antidiabetic therapy,
(2) increase in HbA1c ≥ 0.3% with post-baseline HbA1c > 7%, or
(3) increase in FPG ≥ 20 mg/dL with post-baseline FPG > 130 mg/dL

Dysglycemia Risk: Conclusions

- OCA 25 mg accelerated conversion to incident diabetes and prediabetes, and hastened loss of glycemic control in diabetic subjects
- The impact of this treatment-related dysglycemia on the clinical course of NASH subjects is unknown due to the lack of a causal mechanism underlying the hyperglycemia

PRURITUS

Pre-Specified Interventions for Pruritus

- Pruritus ≥Grade 1 in severity – topical intervention
- Pruritus ≥Grade 2 in severity – consider one or more of the following:
  - Drug holiday or less frequent dosing (every other day dosing, interrupting treatment)
  - Use of bile acid sequestrants (BAS) – if after four to six weeks of BAS therapy still unable to tolerate OCA, then recommendation to discontinue OCA
- Pruritus ≥Grade 3 (Severe)– study drug discontinuation

Pruritus Occurred in Higher Frequency in Subjects of the OCA 25 mg Treatment Arm

Adverse Events of Special Interest	OCA 25 mg N=827 n [IR per 100 PY]	Placebo N=825 n [IR per 100 PY]	IR Difference (95% CI) per 100 PY
Pruritus	476 [36.5]	221 [10.2]	26.3 (22.7, 29.8)
Severe pruritus	57 [2.3]	3 [0.1]	2.2 (1.6, 2.8)

Source: Statistical reviewer's analysis based on Applicant-submitted data, adtte.xpt.
On-Treatment + 30 days Analyses
Abbreviations: CI, confidence interval; IR, incidence rate per 100 PY; IR Difference, incidence rate difference between OCA and placebo; OCA, obeticholic acid; PY, patient-years of follow-up until the earliest date of study discontinuation, loss of follow-up, 30 days after the last dose of treatment, first event, or death

Management Strategies for Pruritus: More Frequent for OCA Cohort

Pruritus Adverse Event Management	OCA 25 mg (N=827) n (%)	Placebo (N=825) n (%)
Patients with Pruritus	476 (58%)	221 (27%)
Actions Taken with Study Drug (all grades)		
Drug Interruptions	133 (16%)	17 (2%)
Drug Withdrawal	100 (12%)	8 (1%)
Changes in Dose Frequency	38 (5%)	4 (0.5%)
Actions Taken for Treatment of Grades ≤ 2 Pruritus		
Discontinuation from study	21 (3%)	1 (0.1%)
Medications Given	296 (36%)	61 (7%)

On-Treatment +30 days Analysis
Source: Adapted from Applicant's 747-303 Clinical Study Report, Table 45

Conclusions-Safety
(Other than DILI)

- OCA-associated cholelithiasis
  - Increased morbidity
  - Increased number of procedures (e.g., cholecystectomy and endoscopic retrograde cholangiopancreatography (ERCP))
- OCA increased serum LDL-C
  - Required initiation or intensification of statins
- OCA hastened the development of glucose intolerance
  - Required earlier pharmacologic intervention
- OCA-associated pruritus
  - Frequent OCA discontinuation
  - Additional symptomatic drug therapy for pruritus

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BENEFIT:RISK

Ruby Mehta, MD
Team Leader
DHN-OII-OND-CDER-FDA

Comparing Findings From Original Submission and Resubmission

- Original submission
  - Efficacy based on central read methodology suggested modest treatment effect for improvement of fibrosis and no worsening of NASH
  - Serious risks identified based on N=1968 subjects with 2,395 PY of exposure in Study 747-303
  - Determination: Unfavorable benefit-risk assessment
- Resubmission
  - Efficacy (consensus method) has not changed from original submission
  - Serious risks identified in original submission continue to be a concern with greater precision in risk estimates due to a larger safety database (N=2477 subjects with 7,886 PY of exposure)
  - Benefit-risk assessment remains a concern

Summary of Efficacy

- OCA 25 mg demonstrated superiority to placebo on one of the two Month 18 primary endpoints, “improvement of fibrosis and no worsening of NASH”
  - Estimated risk difference (95% CI) ranged from 8.6% (4.2%, 13.0%) to 12.8% (7.0%, 18.5%) across different analyses
- OCA 25 mg failed to demonstrate superiority to placebo on “resolution of NASH and no worsening of fibrosis”
- OCA 10 mg failed to demonstrate superiority to placebo on either of the two Month 18 primary endpoints
- There is uncertainty how the magnitude of change on a surrogate endpoint may translate to meaningful changes in clinical outcomes

Summary of Safety

- Treating **1,000 patients** with OCA 25 mg for **1 year** would translate to approximately:

2.4	additional DILI of ≥ moderate severity	(95% CI of [0.4 to 4.5] additional events)
11	additional DILI of ≥ mild severity	(95% CI of [6.2 to 16] additional events)
263	additional patients with pruritus*	
22	additional patients with severe pruritus*	
198	additional patients with dyslipidemia*	
12	additional patients with gallbladder disease and related complications	
8	additional patients with cholecystectomy	

- Treating 1,000 patients for 2 years would approximately double these additional outcomes

*Based on On-Treatment + 30 days analysis

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Benefit-Risk Considerations and Clinical Implications

OCA for NASH with stage 2 or 3 fibrosis	Benefit Assessment	Fibrosis	Modest efficacy on surrogate endpoint Uncertainty about clinical benefit
		Steatohepatitis	No efficacy demonstrated
	Risk Assessment	Drug-induced liver injury	Frequent laboratory evaluations
		Cholelithiasis and related complications	OCA is lithogenic, increase rates of invasive procedures
		Dyslipidemia	OCA treated subjects required statins sooner and more frequently
		Dysglycemia	Steady deterioration of glycemic control
		Pruritus	Treatment discontinuation and polypharmacy
	Treatment Consideration	Treatment discontinuation in subjects that progress to cirrhosis	Non-invasive tests lack accuracy in identifying disease progression Drug failed to demonstrate efficacy in cirrhotic population Risk of adverse events

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Obeticholic Acid for the Treatment of Adult Patients with Pre-cirrhotic Liver Fibrosis due to Non-Alcoholic Steatohepatitis (NASH)

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting
May 19th, 2023

Charge to the Committee

Frank A Anania, MD
Acting Director,
Division of Hepatology and Nutrition (DHN)
Office of New Drugs
CDER, FDA

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Applicant's Proposed Indication and Doses

- Applicant's Proposed Indication:
  - Treatment of adult patients with pre-cirrhotic liver fibrosis due to Nonalcoholic Steatohepatitis (NASH)
- Proposed Dosage Regimen:
  - OCA 25 mg, orally, once a day

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Original NDA Complete Response: Efficacy

- OCA 25 mg met one of the surrogate endpoints
  - One stage reduction in fibrosis AND no worsening of NASH, treatment difference of 11.1% (95% CI: 5.3%, 17.0%)
- OCA 25 mg failed to meet the second surrogate endpoint
  - NASH resolution AND no worsening of fibrosis
- OCA 10 mg failed to meet either surrogate endpoint

Original NDA Complete Response: Safety Concerns

- Serious drug-induced liver injury (DILI) events
- Cholelithiasis and related complications
- Pruritus requiring symptomatic treatment or OCA discontinuation
- Worsening of LDL cholesterol requiring initiation or intensification of statins
- Worsening of glycemic control, requiring addition of anti-diabetic drugs earlier

Comparing Findings From Original Submission and Resubmission

- Original submission
  - Efficacy based on central read methodology suggested modest treatment effect for improvement of fibrosis and no worsening of NASH
  - Serious risks identified based on N=1968 subjects with 2,395 PY of exposure in Study 747-303
  - Determination: Unfavorable benefit-risk assessment
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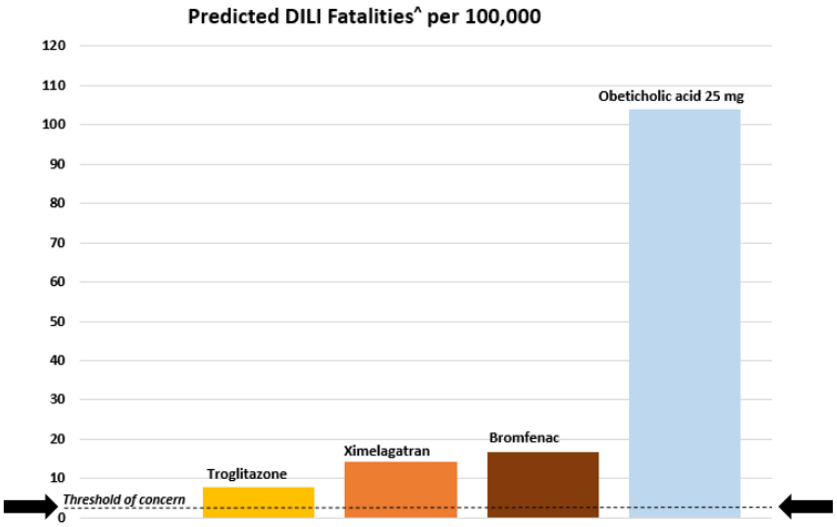
*Based on On-Treatment + 30 days analysis

DILI Fatality Rates and Historical Context



^Fatality = death or liver transplant due to DILI

*FDA Guidance for Industry Drug-Induced Liver Injury: Premarket Clinical Evaluation 2009. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

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Benefit-Risk Considerations

- Uncertainty with identifying appropriate NASH patients:
  - NASH patients with Stage 2 or 3 fibrosis eligible for OCA treatment
  - Identify patients to discontinue OCA because they have progressed to cirrhosis:
    - OCA 25 mg failed to meet its primary endpoint of one stage reduction of fibrosis in subjects with cirrhosis due to NASH, Applicant conducted this as a separate trial*
    - At present non-invasive tests (NITs) may lack precision to distinguish Stage 3 fibrosis from Stage 4 fibrosis (cirrhosis)
    - Unfavorable benefit-risk in patients with cirrhosis
- The benefit-risk of OCA 25 mg remains a concern for the proposed indication despite the new information submitted

www.fda.gov *https://ir.interceptpharma.com/news-releases/news-release-details/intercept-pharmaceuticals-announces-reverse-phase-3-study 114

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Discussion Points

1. Discuss the strength of the available efficacy data on the histopathologic endpoint, a surrogate endpoint that is reasonably likely to predict clinical benefit, in NASH patients with Stage 2 or 3 fibrosis treated with OCA 25 mg.

Discussion Points

2. Based on the data presented, concerning cholestatic drug-induced liver injury (DILI) in OCA 25 mg-treated patients, discuss:
   - Whether periodic liver enzyme monitoring could adequately mitigate the risk of DILI;
   - The frequency of such monitoring; and
   - What stopping criteria should be developed to aid clinicians' decisions to discontinue treatment.

Voting Question #1

1. VOTE: (Yes/No/Abstain)

Given the available efficacy and safety data, do the benefits of OCA 25 mg outweigh the risks in NASH patients with Stage 2 or 3 fibrosis?

- Provide the rationale for your vote

Voting Question #2

2. Vote (Select either (A) or (B)/ Abstain)

Clinical outcome events in patients enrolled in Trial 747-303 will continue to be captured to evaluate clinical benefit in support of a future application for traditional approval. At present, which of the following would you recommend:

(A) Approval of OCA 25 mg at this time, under the accelerated (approval) pathway, based on efficacy data on a histopathologic surrogate and available clinical safety data;

OR

(B) Defer approval until clinical outcome data from Trial 747-303 are submitted and reviewed at which time the traditional approval pathway could be considered?

- Provide the rationale for your vote

Backup Slides Shown

Month 18 Primary Endpoint Results (Odds Ratio) Improvement of Fibrosis and No Worsening of NASH

	OCA 10 mg	OCA 25 mg	Placebo	Odd Ratio 10 mg vs. Placebo (95% CI)	Odds Ratio 25 mg vs. Placebo (95% CI)	P-Value 10 mg	P-Value 25 mg
ITT_old							
Central method (original results)	N=312	N=308	N=311				
N (%)	55 (17.6)	71 (23.1)	37 (11.9)	1.5 (1.0, 2.2)	1.9 (1.3, 2.8)	0.0446	0.0002*
Consensus method	N=312	N=308	N=311				
N (%)	44 (14.1)	69 (22.4)	30 (9.6)	1.5 (0.9, 2.3)	2.3 (1.6, 3.5)	0.0863	<0.0001*
ITT_histology							
Consensus method	N=532	N=539	N=536				
N (%)	86 (16.2)	113 (21.0)	66 (12.3)	1.3 (1.0, 1.8)	1.7 (1.3, 2.2)	N/A	N/A

Source: Statistical analyst's analysis of adsl.xpt, admi.xpt, and adbx.xpt datasets; same as Applicant's results. P-values calculated using CMH test stratified by randomization strata (diabetes at enrollment [yes/no] and use of TZDs or vitamin E at baseline [yes/no]). The Mantel-Haenszel method was used to construct the CIs.
* denotes statistical significance.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Abbreviations: CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; OCA, obeticholic acid

Month 18 Primary Endpoint Results (Analysis Population Defined by Consensus Method)

All Randomized Subjects Expected to Complete Month-18 Visit Under Protocol Version 8 or Earlier and Baseline Fibrosis Stage 2 or 3 Based on the Consensus Method

Endpoint	OCA 10 mg N=409 n (%)	OCA 25 mg N=413 n (%)	Placebo N=427 n (%)	Risk Difference 10 mg-Placebo (95% CI)	Risk Difference 25 mg-Placebo (95% CI)
Improvement of fibrosis and no worsening of NASH	62 (15.2)	101 (24.5)	50 (11.7)	3.4 (-1.2, 8.1)	12.7 (7.5, 17.8)
Resolution of NASH and no worsening of fibrosis	29 (7.1)	40 (9.7)	19 (4.4)	2.6 (-0.6, 5.7)	5.2 (1.7, 8.6)

Source: Applicant's response to Information Request on April 5, 2023.
Note: 95% confidence intervals cannot be used to determine statistical significance.

Results for Additional Efficacy Endpoints: No Worsening of Fibrosis at Month 18 (Consensus Method)

	OCA 10mg	OCA 25mg	Placebo	Odds Ratio 10mg (95% CI)	Odds Ratio 25mg (95% CI)	Risk Difference 10mg-Placebo (95% CI)	Risk Difference 25mg-Placebo (95% CI)
ITT_Old Consensus, n (%)	N=312 203 (65.1)	N=308 201 (65.3)	N=311 189 (60.8)	1.1 (0.9, 1.2)	1.1 (1.0, 1.2)	4.2 (-3.3, 11.8)	4.5 (-3.1, 12.1)
ITT_Histology Consensus, n (%)	N=532 317 (59.6)	N=539 314 (58.3)	N=536 306 (57.1)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	2.5 (-3.4, 8.4)	1.1 (-4.8, 7.0)

Source: statistical analyst's analysis of adsl.xpt and admi.xpt; missing data is imputed as a non-response in datasets
Note: 95% confidence intervals cannot be used to determine statistical significance.

Results for Additional Efficacy Endpoints (ITT_Histology, Consensus Method)

ITT_Histology	OCA 10 mg (N=532)	OCA 25 mg (N=539)	Placebo (N=536)	Risk Difference OCA 10 mg- Placebo (95% CI)	Risk Difference OCA 25 mg- Placebo (95% CI)
Improvement of fibrosis by ≥1 stage	128 (24.1%)	152 (28.2%)	99 (18.5%)	5.6% (0.7%, 10.5%)	9.7% (4.7%, 14.7%)
Improvement of fibrosis by ≥2 stages	34 (6.4%)	35 (6.5%)	13 (2.4%)	3.9% (1.5%, 6.4%)	4.0% (1.6%, 6.4%)
Improvement of fibrosis by ≥1 stage AND resolution of NASH	21 (3.9%)	23 (4.3%)	7 (1.3%)	2.6% (0.7%, 4.5%)	2.9% (1.0%, 4.9%)
No worsening of fibrosis AND no worsening of NASH	193 (36.3%)	210 (39.0%)	169 (31.5%)	4.7% (-1.0%, 10.4%)	7.4% (1.7%, 13.1%)
Improvement of NASH Histological Features					
Steatosis	168 (31.6%)	204 (37.8%)	121 (22.6%)	9.0% (3.7%, 14.3%)	15.3% (9.8%, 20.7%)
Lobular Inflammation	122 (22.9%)	125 (23.2%)	115 (21.5%)	1.5% (-3.5%, 6.5%)	1.7% (-3.2%, 6.7%)
Hepatocellular ballooning	95 (17.9%)	103 (19.1%)	91 (17.0%)	0.8% (-3.7%, 5.4%)	2.1% (-2.5%, 6.7%)

Source: Applicant's Study Report; verified by statistical analysts' analysis of adsl.xpt, admi.xpt.
Note: 95% confidence intervals cannot be used to determine statistical significance.
Baseline and post-baseline NASH CRN steatosis, lobular inflammation, and hepatocellular ballooning were based on the reading of biopsy slides using the Consensus Method
Risk Difference=Percentage of responders in active treatment group - Percentage of responders in placebo, stratified by baseline diabetes status (yes/no) and use of TZDs or vitamin E at baseline (yes/no); the Mantel-Haenszel method was used to construct the CIs.

Adverse Events of Special Interest by Treatment Group
Treatment + 30 days

Adverse Events of Special Interest	Stage 1 Fibrosis		Stages 2 and 3 Fibrosis	
	OCA 25 mg N=97	Placebo N=97	OCA 25 mg N=730	Placebo N=728
	PY n[EAIR] EAIR Diff. (95% CI)	PY n[EAIR]	PY n[EAIR] EAIR Diff. (95% CI)	PY n[EAIR]
Pruritus	166.5 60 [36.0] 29.5 (20.0, 39.0)	321.1 21 [6.5]	1139.3 416 [36.5] 25.7 (21.9, 29.5)	1844.9 200 [10.8]
Moderate pruritus	257.5 32 [12.4] 11.1 (6.6, 15.6)	377 5 [1.3]	1657 233 [14.1] 11.7 (9.7, 13.6)	2236.8 54 [2.4]
Severe pruritus	321.9 8 [2.5] 2.5 (0.8, 4.2)	390.5 0	2183.2 49 [2.2] 2.1 (1.5, 2.8)	2347.4 3 [0.1]
Hepatic Disorder	287.8 20 [7.0] 2.1 (-1.8, 5.9)	347 17 [4.9]	1962.2 144 [7.3] -1.4 (-3.2, 0.4)	1993.5 174 [8.7]
Dyslipidaemia	165.1 48 [29.1] 20.8 (12.0, 29.6)	313.5 26 [8.3]	1203.1 342 [28.4] 19.6 (16.3, 22.9)	1895.4 167 [8.8]
Hyperglacaemia/New Onset Diabetes	244.0 28 [11.5] 4.6 (-0.53, 9.7)	333.4 23 [6.9]	1741.6 173 [9.9] 1.2 (-0.8, 3.2)	1907.9 167 [8.8]
Gallbladder Disease and Related Complications	305.1 6 [2.0] -0.2 (-2.3, 2.0)	372.2 8 [2.2]	2061.1 57 [2.8] 1.7 (0.8, 2.5)	2301.5 25 [1.1]
Severe Gallbladder Disease and Related Complications	318.3 3 [0.9] 0.4 (-0.9, 1.7)	385 2 [0.5]	2160 20 [0.9] 0.8 (0.3, 1.2)	2341.3 4 [0.2]

Source: Generated by FDA Statistical Team

PY: Patient-year until first AESI
[EAIR] indicates incidence rate per 100 patient-year (PY)
EAIR Diff.: incidence rate difference between OCA and placebo

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Adverse Events of Special Interest by Treatment Group
(Treatment +30 days)

Adverse Events of Special Interest	Stage 1 Fibrosis		Stages 2 and 3 Fibrosis	
	OCA 25 mg N=97	Placebo N=97	OCA 25 mg N=730	Placebo N=728
	PY n[EAIR] EAIR Diff. (95% CI)	PY n[EAIR]	PY n[EAIR] EAIR Diff. (95% CI)	PY n[EAIR]
Pancreatitis	322.3 1 [0.3] 0.3 (-0.3, 0.9)	390.5 0	2188.9 7 [0.3] 0.02 (-0.3, 0.3)	2346.7 7 [0.3]
Moderate Pancreatitis	322.3 1 [0.3] 0.3 (-0.3, 0.9)	390.5 0	2191.7 3 [0.1] 0.01 (-0.2, 0.2)	2347.5 3 [0.1]
Severe Pancreatitis	322.3 1 [0.3] 0.3 (-0.3, 0.9)	390.5 0	2191.5 5 [0.2] 0.06 (-0.2, 0.3)	2347 4 [0.2]
MACE (Core)	322.6 1 [0.3] 0.05 (-0.7, 0.8)	390.5 1 [0.3]	2185 10 [0.5] 0.1 (-0.3, 0.5)	2343 8 [0.3]
Adjudicated DILI (Possible/Prob/Highly Likely Causality and >/= Moderate Severity)	323 0	390.5 0	2190.3 8 [0.4] 0.4 (0.1, 0.6)	2347.7 0
Adjudicated DILI (Possible/Prob/Highly Likely Causality and >/= Mild Severity)	316.5 4 [1.3] 1.0 (-0.3, 2.3)	389.9 1 [0.3]	2154.1 35 [1.6] 1.2 (0.6, 1.8)	2335 9 [0.4]
Death	323 1 [0.3]	390.5 1 [0.3]	2195.8 9 [0.4]	2347.7 7 [0.3]

Source: Generated by FDA Statistical Team using

PY: Patient-year until first AESI
[EAIR] indicates incidence rate per 100 patient-year (PY)
EAIR Diff.: incidence rate difference between OCA and placebo

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Table 9. Deaths Across OCA Drug Development Program

Trial	OCA 10 mg N=917	OCA 25 mg N=1009	Placebo N=1017
747-303	11	14	10
747-209 including LTSE*	1	1	0
DS8602001	0	0	0
FLINT Trial	0	2	0
Total number of deaths in NASH drug development program	12	17	10

Source: Statistical reviewer analysis based on Applicant submitted data adsl.xpt and the supporting document number 001 (Applicant submitted on September 26, 2019).
Abbreviations: LTSE, long-term safety extension; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid

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Post-Baseline LDL-C Categorical Increases Study 747-303

Adverse Event	OCA 10 mg N=825 n (%)	OCA 25 mg N=827 n (%)	PBO N=825 n (%)
LDL-C >100 mg/dL	736 (89.2)	738 (89.2)	666 (80.7)
LDL-C >130 mg/dL	562 (68.1)	606 (73.3)	454 (55.0)
LDL-C >190 mg/dL	167 (20.2)	210 (25.4)	77 (9.3)

Source: Study 747-303 Clinical Study Report, Table 79.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; OCA, obeticholic acid

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