Clinical Study Protocol 747-401

OBETICHOLIC ACID (OCA)

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

EudraCT Number: 2017-001762-13

ClinicalTrials.gov Identifier: NCT03633227

Sponsor

Intercept Pharmaceuticals, Inc.

305 Madison Avenue

Morristown, NJ 07960

USA

16.1.1 PROTOCOL AND AMENDMENTS

Protocol 747-401, Version 1, dated 20 Dec 2016

Protocol 747-401, Version 2, dated 22 May 2017

Protocol 747-401, Version 3, dated 04 Jan 2018

Protocol 747-401, Version 4, dated 15 Feb 2019

Protocol Addendums

Addendum 1 to Protocol 747-401, dated 19 May 2020

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Version 1: 20 December 2016

(For FDA Review Only)

Sponsor

Intercept Pharmaceuticals, Inc.
4760 Eastgate Mall
San Diego, CA 92121
USA

TEL: PPD

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD PhD

Vice President, Clinical Development
Intercept Pharmaceuticals, Inc.

12/20/16
Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-401. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected patients according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-401 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human patients in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; (6-ECDCA); INT-747; DSP-1747

Title of Study:

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

Investigators and/or Study Center(s):

The study is planned to have approximately 20 investigational sites, globally.

Studied Period: The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete the primary treatment period at which point all patients will transition to an open-label long-term safety extension (LTSE).	**Phase of Development:** Phase 4

Objectives: In patients with Moderate to Severe PBC:

Primary Objective:

- To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and OCA glucuronide
- To evaluate the safety and tolerability of OCA treatment compared with placebo

Secondary Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - The model of end stage liver disease (MELD) score and its components
  - Child-Pugh (CP) score and its components
  - Liver biochemistry including bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT])
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma and fecal bile acids

Additional Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - Markers of inflammation
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF] score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])

- To assess clinical outcomes consistent with end-stage liver disease (eg, liver -related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, hepatocellular carcinoma)
- To assess the PK/Pharmacodynamic (PD) relationship of OCA on:
  - ALP, total bilirubin, and aminotransferases
  - Bile acid homeostasis
  - Safety and tolerability (eg pruritus)

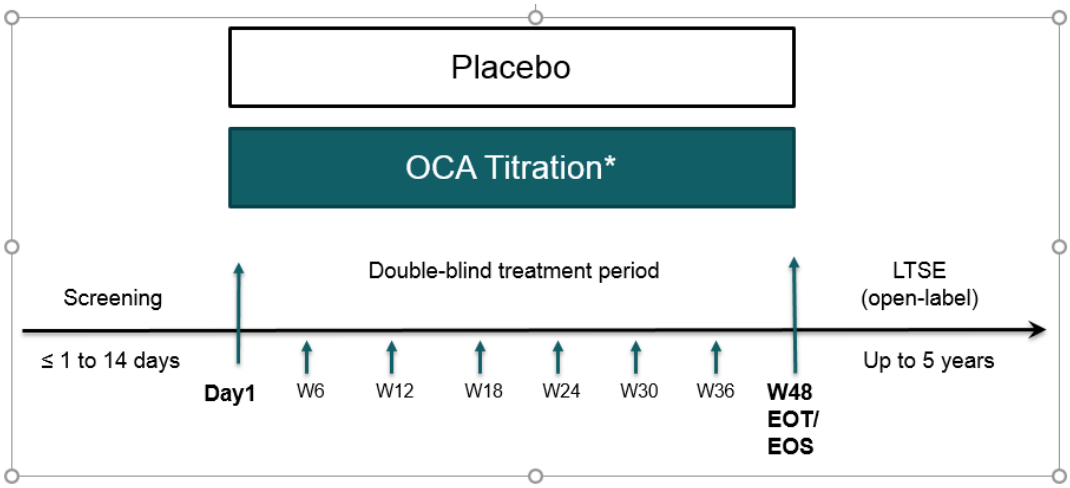
Methodology: This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with PBC with moderate to severe hepatic impairment defined as Child-Pugh B (CP-B) (moderate) and Child-Pugh C (CP-C) (severe) including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened for up to ≤14 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Primary Treatment Period: During the primary treatment period (ie, Day 1 through Week 48), clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD (trough). At each visit, trough PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12 and only after a patient uptitrates. Following completion of the Week-48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the 48-week primary treatment period.

Long -term Open Label Extension Phase: Once all patients have completed the double-blind 48-week primary treatment period, patients will have the option to continue into an open-label long-term safety extension and all patients will receive OCA. Visits in the LTSE will occur every 3 months for up to 5 years. Patients on placebo during the primary treatment period will initiate study medication at 5-mg OCA once weekly and follow the dosing regimen based on their CP score. Patients on OCA during the primary treatment period will continue the dose that they are on once unblinded.

Study Design Diagram



EOS = end of study; EOT = end of treatment, OCA = obeticholic acid

*Initial dose titration of investigational product may occur at the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score.

Dosing Regimen:

All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. Starting at Week 12, safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below:

- At Week 12, if investigational product is tolerated and laboratory assessments from the Week 6 visit do not indicate a safety concern, the patient will change the dosing frequency to 5 mg twice weekly, at least 3 days apart.
- Following an additional 6 weeks of treatment, if investigational product is tolerated, patients may be up-titrated to OCA 10 mg twice weekly at least 3 days apart, the maximum dose for patients with CP-C.
- Following an additional 6 weeks of treatment, if tolerated, patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, the maximum dose for patients with CP-B.
- If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply.

Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score

	Child-Pugh B (Moderate Hepatic Impairment)		**Child-Pugh C (Severe Hepatic Impairment)**	
	Treatment Group		**Treatment Group**	
	OCA	Placebo	OCA	Placebo
Starting Dose[a] (Day 1)	5 mg once weekly	matching placebo	5 mg once weekly	matching placebo
Titration 1[b] (≥Week 12)	5 mg twice weekly[c]	matching placebo	5 mg twice weekly[c]	matching placebo
Titration 2[b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]	matching placebo	10 mg twice weekly[c]	matching placebo
Titration 3[b] (≥6 weeks after Titration 2)	5 mg once daily	matching placebo	NA	matching placebo

[a] Starting dose based on patient's Child-Pugh Score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.
[c] Dosing per the twice weekly schedule must be at least 3 days apart.

Number of Patients (planned): Approximately 50 patients will be enrolled in this study.

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines, defined as having ≥2 of the following 3 diagnostic factors:

– History of elevated ALP levels for at least 6 months

– Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (<1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)

- Liver biopsy consistent with PBC (collected at any time prior to Screening)

2. Evidence of cirrhosis including at least one of the following:
   - Biopsy indicating cirrhosis or a medical history with histological evidence of cirrhosis
   - Clinical evidence consistent with cirrhosis including: esophageal varices, ascites, encephalopathy, or portal hypertension
   - Liver stiffness as assessed by TE of >16.9kPa
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening (ie, within 14 days before the first dose of investigational product):
   - Moderate: CP-B (Scores 7 to 9) or
   - Severe: CP-C (Scores 10 to12)
4. MELD score of 6 to 24 at Screening
5. Age ≥18 years
6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate UDCA (no UDCA for ≥3 months)
7. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) with spermicide **or** (b) diaphragm, with spermicide; or
   - Intrauterine device; or
   - Vasectomy (partner), or
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection, or
   - Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)
8. Must provide written informed consent and agree to comply with the study protocol.

Key Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant, organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection, RNA positive
   - Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the medical monitor
   - Primary sclerosing cholangitis
   - Alcoholic liver disease
   - Definite autoimmune liver disease or overlap hepatitis
   - Gilbert's Syndrome
5. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function during the Screening period
6. Patients with history or presence of hepatorenal or hepatopulmonary syndrome
7. Patients with significant active infection (ie spontaneous bacterial peritonitis)

8. Patients with known or suspected hepatocellular carcinoma
9. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
10. Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study
11. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
12. UDCA naïve (unless contraindicated).

Investigational Product, Dosage and Mode of Administration:

OCA 5 mg or OCA 10 mg tablets, oral administration

Placebo tablets, matched in size and appearance to OCA tablets, oral administration

Duration of Treatment: The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the double-blind 48-week primary treatment period. Hence, depending on the rate of patient enrollment, patients will be exposed to investigational product for a minimum of 1 year up to approximately 2 years during the blinded period. Following completion of the blinded period, patients will have the option to continue into an extension during which they will receive open-label treatment and be seen at regular visits every 3 months for up to 5 years.

Criteria for Evaluation:

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates, glyco-OCA, tauro-OCA, and OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus and fatigue
Secondary Objectives	**Assessments**
Changes in Risk Scores	Changes in MELD and CP Score components
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma, fecal bile acids
Additional Objectives	**Assessments**
Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30, and others as determined during course of study.
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	Transient Elastography and ELF (including HA, P3NP, and TIMP-1)
PK/PD relationship of OCA and liver biochemistry	OCA and its conjugates, glyco-OCA tauro-OCA; and OCA glucuronide
PK/PD relationship of OCA and bile acid homeostasis	Bile acids
Patient reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
PK/PD relationship of OCA: Markers of safety and tolerability	Pruritus and fatigue

Clinical outcomes	Incidence and time to first occurrence of any of the following: all-cause mortality, liver-related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, hepatocellular carcinoma

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; HDL = high density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IgA = immunoglobulin; A IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; MACE = Major Adverse Cardiovascular Events; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PD = pharmacodynamic; PK = pharmacokinetic; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; SAE = serious adverse event; TNF-α = tumor necrosis factor-α, VAS = visual analog scale

Statistical Methods:

Analysis Populations:

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK Population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

Pharmacokinetic Analyses:

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, OCA glucuronide and potentially other conjugates or metabolites not yet identified.

PK analysis will based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.

Safety Analyses:

Safety analyses will be conducted using the Safety population. Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will be summarized by treatment group. The treatment-emergent AEs (TEAEs) and serious AEs (SAEs) will be tabulated by system organ class and preferred term for each treatment group, and similarly by severity and relationship to treatment. Laboratory parameters, physical examinations including vital signs, and electrocardiograms will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. No inferential comparison of safety endpoints will be performed.

Efficacy Analyses:

This study does not plan to test a formal hypothesis for any efficacy endpoint.

The endpoints of efficacy assessments are change in bilirubin, INR, creatinine, albumin, platelets, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Additional Efficacy Analyses

Analyses of changes in liver stiffness and ELF, cytokeratin-and TIMP-1, and markers of inflammation will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.

The following clinical outcomes will be captured in the study:

- All-cause mortality
- Liver related death
- Liver transplant
- Variceal bleed
- Hepatic encephalopathy
- Bacterial peritonitis
- Ascites
- Hepatocellular carcinoma

The incidence and time to first occurrence of any of the above listed clinical outcomes will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians and corresponding 95% confidence intervals (CIs), if the medians can be estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the time to each of the above outcomes will be summarized by treatment group using the same methods as defined above.

Sample Size Justification:

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients per OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. The assessment was based on 80% powering for the 90% confidence interval of the geometric mean ratio of Total OCA (sum of OCA, glyco OCA, and tauro OCA).

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
6-ECDCA	6α-ethyl chenodeoxycholic acid (also known as INT-747)
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
BP	blood pressure
C4	7α-hydroxy-4-cholesten-3-one
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CK-18-M30	cytokeratin-18 neoepitope M30
CLDQ	Chronic Liver Disease Questionnaire
CRA	Clinical Research Associate
eCRF	electronic case report form
Hs-CRP	high sensitivity C-reactive protein
CP	Child-Pugh
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
ET	Early termination
FDA	Food and Drug Administration

Abbreviation or Specialist Term	Explanation
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid
HCP	Health care professional
HDLc	high density lipoprotein
IB	Investigational Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
ITT	intent-to-treat
IWRS	interactive web response system
KM	Kaplan-Meier
LDLc	low density lipoprotein
LTSE	Long-term safety extension
LS	Least squares
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model of end stage liver disease
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or Specialist Term	Explanation
SAR	suspected adverse reaction
SD	standard deviation
SI	standard international system of units
SOC	System organ class
SUSAR	suspected unexpected serious adverse reaction
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
the Sponsor	Intercept Pharmaceuticals, Inc.
TNF-α	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States (of America)
VAS	Visual Analogue Scale
VLDL	very low density lipoprotein

5. INTRODUCTION

5.1. Overview of Disease State and OCA

Primary Biliary Cholangitis, (PBC, also known as primary biliary cirrhosis [Beuers 2015a, Beuers 2015b, Beuers 2015c]) is a serious, life-threatening, cholestatic liver disease of unknown etiology that, without treatment, frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and necessitates liver transplantation or results in death. PBC is a rare disease with reported prevalence in the US of 40.2/100,000 (Kim 2000). PBC disproportionately affects women approximately 10:1 and is typically diagnosed in patients between 40 to 60 years of age.

Ursodeoxycholic acid (UDCA), a physiological constituent of human bile, was approved in 2004 for treatment of PBC (Lindor 2009). While UDCA therapy had a marked effect on the treatment of PBC, up to 50% of patients showed a suboptimal response or no response to UDCA. Such patients were at significantly increased risk of a poor clinical outcome due to PBC disease progression. Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist and modified bile acid is derived from the primary human bile acid chenodeoxycholic acid (CDCA), was developed for the treatment of PBC and to provide patients with an inadequate response to or poor tolerance of UDCA a novel treatment option that was safe and effective. In May 2016, the United States Food and Drug Administration granted accelerated approval for OCA (marketed as OCALIVA®), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for OCALIVA® for the same indication.

5.2. Clinical Development of Obeticholic Acid

As of 31 Jan 2016, approximately 1726 patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 458 patients had PBC, 330 patients had nonalcoholic steatohepatitis, 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease, 33 patients had alcoholic cirrhosis/portal hypertension, and 20 patients had primary sclerosing cholangitis (PSC).

Overall, the pharmacokinetic (PK) profile of OCA is consistent with that expected of a bile acid. Phase 1 studies demonstrated that OCA is rapidly absorbed and extensively conjugated with glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates are primarily eliminated via biliary excretion, and plasma concentration time profiles demonstrated multiple peaking with prolonged exposure, indicative of enterohepatic circulation. Plasma concentrations of OCA and its conjugates spike shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.

The OCA clinical development program was based on a wide range of studies in PBC patients and healthy volunteers. The clinical pharmacology studies supported the proposed dosing regimen: 10-mg fixed dose and a titration regimen starting at OCA 5 mg with titration to 10 mg based on clinical and biochemical response. The clinical program included a pivotal Phase 3 clinical study (747-301) and 2 Phase 2 clinical studies (747-201 and 747-202), which formed the primary basis of approval of OCA.

Study 747-201 (59 patients) evaluated 2 doses of OCA (10 mg and 50 mg) given as monotherapy versus placebo. Statistically significant and clinically relevant relative and absolute reductions from Baseline in alkaline phosphatase (ALP) were achieved with both doses of OCA versus placebo ($p < 0.0001$). Mean relative ALP reductions were 44.5% (OCA 10 mg) and 37.6% (OCA 50 mg) compared to an increase of 0.4% with placebo. Further, significant improvements in gamma-glutamyl transferase (GGT) and in conjugated bilirubin were observed with both doses compared with placebo ($p < 0.05$). OCA also resulted in decreased circulating alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Study 747-202 (165 patients) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in patients on a stable therapeutic dose of UDCA. Overall, the data from 747-202 were consistent with Study 747-201. Statistically significant and clinically meaningful relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p < 0.0001$). Mean ALP reductions from baseline ranged from 21% to 25% compared to 3% with placebo. Improvements were also seen in GGT and ALT levels and in conjugated bilirubin levels.

Study 747-301 (216 patients) was a Phase 3, double-blind, placebo-controlled, parallel-group study followed by a long-term safety extension (LTSE) using OCA in patients with PBC. The primary endpoint for Study 747 301 was a composite endpoint based on the proportion of patients reaching specific criteria for ALP and bilirubin (ALP <1.67x upper limit of normal [ULN] with a ≥15% reduction and bilirubin ≤ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to <1.67x ULN with a ≥15% reduction from baseline and a normal bilirubin level after 12 months of therapy. The placebo group experienced a mean decrease in ALP from baseline of 5%, compared to a significant mean decrease of 39% in the OCA 10 mg dose group and 33% in the OCA titration group (both OCA dose groups $p<0.0001$ versus placebo).

The LTSE phases of both Phase 2 studies and the Phase 3 study support the long-term safety of OCA and demonstrate a durable therapeutic response.

Study 747-302 is an ongoing randomized, double-blind, placebo-controlled clinical outcomes study, designed to confirm the clinical benefit of OCA treatment in patients with PBC. This study is inclusive of patients with early to advanced stage PBC.

5.2.1. Rationale for Study Design

There are limited clinical data available to support the use of OCA in patients with PBC with moderate to severe hepatic impairment. The current recommended dosing of such patients is based on modeled systemic and hepatic concentrations. Therefore, Study 747-401 is specifically designed to characterize the PK, safety, and efficacy effect of OCA in this patient population.

PK and safety parameters will be evaluated as the primary objectives and efficacy parameters will be evaluated as secondary and additional objectives. While the prognostic utility of ALP has been established by the Global PBC study group, increasing levels of bilirubin is more relevant to understanding the progression of end stage liver disease. Consistently, bilirubin is a key marker of advancing disease as characterized by the Global PBC study group as well as its incorporation into MELD, Child-Pugh (CP) and Mayo risk scores. As such, the potential of OCA to stabilize bilirubin levels will be evaluated.

In order to generate data for the patient population in a timely fashion, Study 747-401 is designed with a relatively short-term, 1-year double-blind treatment period to gather primarily PK and safety data. Therefore, the study will not formally test the long-term efficacy of OCA on clinical outcomes.

Although Study 747-401 is not designed to formally evaluate clinical outcomes, these data will be collected and assessed as an additional objective. Given the importance of evaluating clinical outcomes in patients with the most advanced form of the disease, these events will be prospectively adjudicated consistent with the procedures implemented in Study 747-302. This will allow for a more robust meta-evaluation of clinical outcomes in patients with moderate to severe hepatic impairment following the completion of both studies.

Patients with moderate or severe hepatic impairment (Child Pugh B or C) will constitute approximately 20% of the patients included in the ongoing clinical outcomes Study 747-302 which was specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment. Data collected from Study 747-401 will serve as a bridge between the two studies.

Taken together, data from this study will complement the data from Study 747-302 and offer the opportunity to better inform the benefit risk profile and appropriate treatment of hepatically-impaired patients.

5.2.2. Rationale for Obeticholic Acid Dose and Duration

Results from the hepatic impairment study (747-103) indicate that plasma exposure increases, in comparison to subjects with normal liver function, with increasing severity of impairment as classified by Child Pugh A (CP-A), CP-B or Child Pugh C (CP-C) scores by 1.4-, 8.0-, and 13-fold, respectively. No apparent impact on the overall safety profiles were observed in this study. Liver exposure, however, modestly increased by 1.1-, 1.5, and 1.7-fold, respectively, as shown in simulations using a physiologic PK model developed to characterize OCA and its conjugates. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Therefore, a modified dosing regimen is recommended for OCA in patients with moderate and severe hepatic impairment that is designed to initiate doses to achieve plasma exposures levels of OCA similar to those without hepatic impairment or CP-A. After which, subjects may then titrate their doses upwards to achieve liver exposures that would be similar in both patient populations. This modified dosing regimen was selected based on the established safety and tolerability of OCA in subjects with PBC, along with PK/PD modeling and simulations.

Patients will initiate dosing at OCA 5 mg once weekly. Starting at Week 12, if the prior dose regimen was tolerated, the patients will increase the dosing frequency to 5 mg twice weekly (at least 3 days apart). After 6 weeks, a second titration may occur to OCA 10 mg twice weekly as long as tolerated. Patients classified as CP-B may further titrate their dose upwards to OCA 5 mg once daily after 6 weeks on the OCA 10 mg twice weekly regimen.

5.2.3. Rationale for Population Chosen

Patients with PBC and moderate or severe hepatic impairment, based on Child-Pugh score and varying levels of MELD (Model of End-stage Liver Disease), are the targeted population for this study as OCA has been studied primarily in early to moderate stages of liver disease in patients with PBC. There is a great need to extend therapies to PBC patients with more advanced liver disease. Given the unmet medical need and observed efficacy, safety and tolerability profile of OCA in early and moderate PBC, evaluating the effects of OCA in a late stage population is warranted.

5.2.4. Rationale for Control Group

Placebo Control Group

The use of a randomized placebo control group added to established standard of care provides the best scientific evidence of efficacy and safety. The use of a placebo control provides a concurrent comparator group, accounting for not only a placebo effect but continued standard of care. The use of a placebo control is critical to assess the safety and tolerability of OCA but also as a comparator for the high rate of clinical outcomes events which are expected in this advanced population.

5.3. Summary of Known Potential Risks with Investigational Product

The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy patients, but with a much lower frequency than that observed in patients with PBC.

Consistent with the dose-limiting hepatic toxicities observed in the non-clinical studies and the chemical characteristics of OCA as a bile acid and detergent, dose-related but reversible and asymptomatic increases in ALT and AST were observed in healthy volunteers treated with multiple doses of OCA starting at the 100 mg dose (Study 747-102).

In patients with chronic liver disease such as PBC, hepatobiliary findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed. These findings were seen more frequently with doses of OCA 10 mg once daily to OCA 50 mg once daily (up to 5x the highest recommended dose). In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.

Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDLc) and an increase in low density lipoprotein (LDLc). Notably, in patients with PBC, the decrease in mean HDLc levels occurred early and stabilized within 3 months after which time levels generally remained constant over the course of treatment. The average levels of HDLc remained within normal limits. Commensurate with decreases in HDLc, decreases in total cholesterol were observed in patients with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA treated patients with the exception of a modest transient and early rise after initiation of treatment.

Based on Studies 747-103 and 747-204 in subjects with hepatic impairment, increased systemic exposure was not associated with an apparent change in the safety profile of OCA as assessed by

the incidence and severity of AEs or by changes in clinical laboratory tests. Hepatotoxicity has been associated with increased liver concentrations of OCA. Hepatic impairment does not affect the ability of OCA to activate FXR in the intestine and the liver.

Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

The study will be conducted in patients with PBC with moderate to severe hepatic impairment defined as CP-B (moderate) and CP-C (severe) with MELD scores ranging from 6 to 24.

6.1. Primary Objectives

- To evaluate the PK of OCA and its conjugates glyco-OCA, tauro-OCA, and OCA glucuronide
- To evaluate the safety and tolerability of OCA treatment compared with placebo

6.2. Secondary Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - The MELD score and its components
  - CP score and its components
  - Liver biochemistry including bilirubin, ALP, and aminotransferases (ALT, AST, and GGT)
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma and fecal bile acids

6.3. Additional Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - Markers of inflammation
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess clinical outcomes consistent with end-stage liver disease (eg, liver-related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, hepatocellular carcinoma)
- The PK/Pharmacodynamic (PD) relationship of OCA on:
  - Liver biochemistry including ALP, total bilirubin, and aminotransferases
  - Bile acid homeostasis
  - Safety and tolerability (eg pruritus)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with PBC with moderate to severe hepatic impairment defined as Child-Pugh B (CP-B) (moderate) and Child-Pugh C (CP C) (severe) including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened for up to ≤14 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

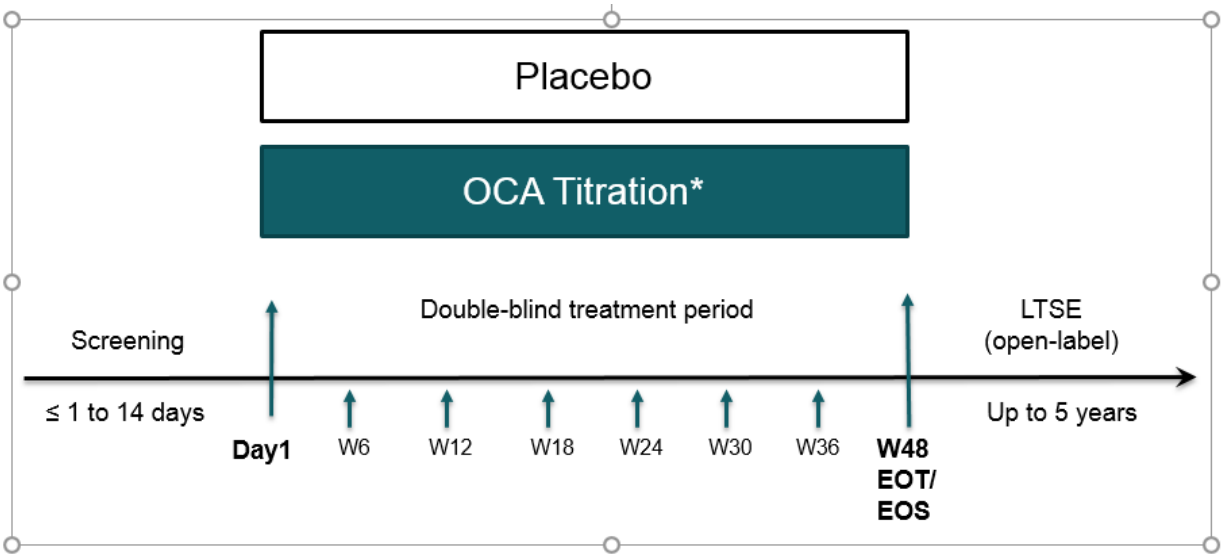
Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Primary Treatment Period: During the primary treatment period (ie, Day 1 through Week 48), clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD (trough). At each visit, trough PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12 and only after a patient uptitrates. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the 48-week primary treatment period.

Long -term Open Label Extension Phase: Once all patients have completed the double-blind 48-week primary treatment period, patients will have the option to continue into an open-label LTSE and all patients will receive OCA. Visits in the LTSE will occur every 3 months for up to 5 years. Patients on placebo during the primary treatment period will initiate study medication at OCA 5-mg once weekly and follow the dosing regimen based on their CP score. Patients on OCA during the primary treatment period will continue the dose that they are on once unblinded. The open-label LTSE study design and study procedures will be described in a separate protocol and statistical analysis plan (SAP).

7.1.1. Study Design Diagram

Figure 1: Study Design



EOS = end of study; EOT = end of treatment; OCA = obeticholic acid
*Initial dose titration of investigational product may occur at the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures (Double-Blind Treatment Period)

	Double-Blind Treatment Period										
			Weeks								
	Screening	Day 1	3 Safety Contact[a]	6	12	18	24	30	36	48	ET/ EOS
Visit Window (+/-)[b]	≤-1 to -14 days		±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	
Fast ≥8 h Prior to Visit[c]		X		X	X	X	X	X	X	X	X
Informed Consent	X										
Medical/PBC History[d]	X										
Inclusion/Exclusion Criteria	X	X									
Physical Exam[e]	X	X		X	X	X	X	X	X	X	X
Vital Signs	X	X		X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X									X	X
MELD	X	X		X	X	X	X	X	X	X	X
Assessments for Child-Pugh Score[f]	X	X		X	X	X	X	X	X	X	X
Patient Questionnaires (Pruritus VAS, PBC-40, EQ-5D-5L, and CLDQ)[g]		X		X	X		X		X	X	X
Randomization/Treatment Assigned		X									

Table 1: Schedule of Study Procedures (Double-Blind Treatment Period) (Continued)

	Double-Blind Treatment Period										
			Weeks								
	Screening	Day 1	3 Safety Contact[a]	6	12	18	24	30	36	48	ET/ EOS
Visit Window (+/-)[b]	≤-1 to -14 days		±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	
Dispense IP[h]		X		X	X	X	X	X	X	X	X
Dose Titration[i]					X	X	X	X	X	X	X
IP Accountability/Compliance			X		X	X	X	X	X	X	X
Urinalysis (dipstick)	X	X								X	X
Urine-based β-hCG Pregnancy Test[j]	X	X		X	X	X	X	X	X	X	X
Virology (HCV/HBsAG)	X										
Serum Chemistry/Hematology/ Coagulation	X	X		X	X	X	X	X	X	X	X
IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK 18 M30, others as determined during course of study		X			X		X		X	X	X
PK trough collection		X	X	X	X	X	X	X	X		
PK serial collection	Will only occur when patient uptitrates. Refer to Section 12 for PK sampling schedules and procedures.										
Fecal PK Analysis											
Bile Acid/C4/FGF-19		X		X	X	X	X	X	X	X	
TE Fibroscan®		X					X			X	X
ELF		X			X		X		X	X	X

AE = adverse event; eCRF = electronic case report form; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope M30; CLDQ = Chronic Liver Disease Questionnaire; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; hs-CRP = high-sensitivity C-reactive protein; IP = Investigational Product; MELD = Model of end stage liver disease; PK = pharmacokinetics; TE = transient elastography; wk(s) = week(s).

[a] Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 3 and continuing to Week 48 to assess for AEs, concomitant medications, and verify that s/he is dosing as directed.

[b] Visits should be based on Day 1.

[c] The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits (except Screening Visit 1) but water is permitted.

[d] Medical history performed at Screening only.

[e] The yearly physical exam will also include an assessment of smoking and alcohol consumption history and current habits for both. Height will only be collected at Day 1 and Week 48.

[f] Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF.

[g] The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the data from that questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease.

[h] Patients will be instructed to begin dosing on the Day 1 visit after completing all study assessments. (ie, on Day 1). Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

[i] Initial dose titration of investigational product may occur at the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score.

[j] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally)

7.1.3. Study Duration

The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the primary treatment period, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete the primary treatment period (Figure 1). Patients will have the option to continue into an open-label LTSE after all patients have completed the Week 48 procedures in which they will receive open-label treatment and be seen at regular visits every 3 months for up to 5 years.

7.2. Number of Patients

Approximately 50 patients will be enrolled in this study.

7.3. Planned Dosing Regimen

All patients will initiate investigational product once weekly with OCA 5-mg or matching placebo.

All patients will initiate investigational product once weekly with OCA 5-mg or matching placebo. Starting at Week 12, safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below (Table 2):

- At Week 12, if investigational product is tolerated and laboratory assessments from the Week 6 visit do not indicate a safety concern, the patient will change the dosing frequency to 5 mg twice weekly, at least 3 days apart.
- Following an additional 6 weeks of treatment, if investigational product is tolerated, patients may be up-titrated to OCA 10 mg twice weekly at least 3 days apart, the maximum dose for patients with CP-C.
- Following an additional 6 weeks of treatment, if tolerated, patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, the maximum dose for patients with CP-B.
- If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply.

Table 2: Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score

	Child-Pugh B (Moderate Hepatic Impairment)		Child-Pugh C (Severe Hepatic Impairment)	
	Treatment Group		Treatment Group	
	OCA	Placebo	OCA	Placebo
Starting Dose [a] (Day 1)	5 mg once weekly	matching placebo	5 mg once weekly	matching placebo
Titration 1 [b] (≥Week 12)	5 mg twice weekly[c]	matching placebo	5 mg twice weekly[c]	matching placebo
Titration 2 [b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]	matching placebo	10 mg twice weekly[c]	matching placebo
Titration 3 [b] (≥6 weeks after Titration 2)	5 mg once daily	matching placebo	NA	matching placebo

[a] Starting dose based on patient's Child-Pugh Score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.
[c] Dosing per the twice weekly schedule must be at least 3 days apart.

7.4. Dose Adjustment Criteria

Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns or as a result of changes in a patient's CP Score.

Dose titrations may involve increases or decreases in dosing frequency or dose and are dependent on tolerability (as assessed by a review of AEs and safety laboratory results). In general, down-titration may be done in response to tolerability concerns and can occur at any time. Up-titration will be done per protocol based on tolerability, as assessed by the Investigator, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated for each dosing regimen as defined in Section 7.3.

Scheduled Dose Titration - The first dose titration for any patient may occur no earlier than 12 weeks following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for patients may occur no earlier than 6 weeks following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability; see Section 7.4.1)

Dose Titration due to Change in Child-Pugh Score – Over the course of the study, a patient's CP category may change. When patients demonstrate a change in CP Score (as assessed per Table 12), dosing should be reassessed and modified if appropriate (Table 2). Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in CP score. Table 3 provides an overview of the possible changes in dosing regimen due to changes in CP Score. Dosing should follow the titration schedule of the new dosing regimen such that the maximum dose within that dosing regimen is ultimately attained, based on tolerability and clinical judgment.

If a patient demonstrates an improvement to CP-A, they should follow the dosing regimen for patients with CP-B.

Table 3: Changes in Dosing Regimen Due to Changes in Child Pugh Score

Original Status	New Status[a]	
	Child-Pugh B **Moderate Hepatic Impairment**	**Child-Pugh C** **Severe Hepatic Impairment**
Child-Pugh B	*No Change*	5 mg daily → 10 mg twice weekly[b] 10 mg twice weekly[b] → No change **or** 5 mg twice weekly 5 mg twice weekly[b] → No change **or** 5 mg once weekly
Child-Pugh C	10 mg twice weekly → 5 mg daily 5 mg twice weekly →No change **or** 10 mg twice weekly[b] 5 mg once weekly →5 mg twice weekly	*No Change*

[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.4.1.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

CP Scores will be calculated at all study visits. While PBC-specific versions of CP scores are available, this study will use the standard calculation (Pugh 1973, Lucey 1997). All associated visit data (including central laboratory results) should be entered into the electronic case report form (eCRF) in a timely fashion to confirm that the patient's CP Score has not changed. If a change in CP Score is observed independent of a study visit, the patient should be contacted via phone to discuss the need for a dosing modification and should be asked to return to the investigative site as soon as possible if a new bottle of investigational product is required to be dispensed.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. A review of AEs and available safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within approximately 6 weeks of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigational product (eg, Week 6, laboratory results should be reviewed prior to titration at Week 12). If for any reason, laboratory results are not available at the time of the planned up-titration visit, additional laboratory samples must be obtained and reviewed, prior to up-titrating the patient to a higher dose.

To be eligible for a dose up-titration, patients should not be experiencing significant AEs that are suspected to be related to investigational product (eg, severe pruritus) or displaying other symptoms that may indicate intolerability of investigational product.

7.4.2. Safety Criteria for Adjustment or Stopping Doses

Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.

Subjects who discontinue investigational product are expected to continue in the study (and follow the regular visit schedule) until the end of the study, and the study will only terminate at the time.

7.5. Criteria for Study Termination

The Sponsor (Intercept Pharmaceuticals, Inc.) reserves the right to terminate the study at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the Data Monitoring Committee (DMC), it may be necessary to stop the study before all patients have completed the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, Good Clinical Practice [GCP] noncompliance or poorly performing sites, as determined by the number of patients enrolled or the quality of the study data).

The Investigator and/or Sponsor (or designee) must notify the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of discontinuation of a site or the study and the reason for doing so.

Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all patients for the end of study (EOS) or end of treatment (EOT) Visit.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Population

This study will be conducted at approximately 20 international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B (moderate) and CP-C (severe). Prospective patients will be identified primarily from the hospital and/or physician's database of patients with PBC, or may be referred from other physicians. Patients may self-refer to an Investigator if they become aware of the study through local, national, or international PBC patient societies, forums, or networks.

8.2. Patient Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines [Lindor 2009, EASL 2009]), defined as having ≥2 of the following 3 diagnostic factors
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (<1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
    - Liver biopsy consistent with PBC (collected at any time prior to Screening)
2. Evidence of cirrhosis including at least one of the following:

- Biopsy indicating cirrhosis or a medical history with histological evidence of cirrhosis
- Clinical evidence consistent with cirrhosis including: esophageal varices, ascites, encephalopathy, or portal hypertension
- Liver stiffness as assessed by TE of >16.9kPa

3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening (ie, within 14 days before the first dose of investigational product):
   - Moderate: CP-B (Scores 7 to 9) or
   - Severe: CP-C (Scores 10 to 12)
4. MELD score of 6 to 24 at Screening
5. Age ≥18 years
6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate UDCA (no UDCA for ≥3 months)
7. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) with spermicide **or** (b) diaphragm with spermicide; or
   - Intrauterine device; or
   - Vasectomy (partner); or
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
   - Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)
8. Must provide written informed consent and agree to comply with the study protocol.

8.3. Patient Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. History or presence of other concomitant liver diseases including:
   a. Hepatitis C virus infection, RNA positive
   b. Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the medical monitor
   c. Primary sclerosing cholangitis

d. Alcoholic liver disease
e. Definite autoimmune liver disease or overlap hepatitis
f. Gilbert's Syndrome

5. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function during the Screening period
6. Patients with history or presence of hepatorenal or hepatopulmonary syndrome
7. Patients with significant active infection (ie spontaneous bacterial peritonitis)
8. Patients with known or suspected hepatocellular carcinoma
9. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
10. Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study
11. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
12. UDCA naïve (unless contraindicated).

8.4. Patient Withdrawal Criteria

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

The following events are considered appropriate reasons for discontinuation of investigational product;

- Patient begins treatment with commercially available OCA
- The Investigator or Sponsor considers that it is advisable or in the best interest of the patient
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to investigational product
- Patient undergoes liver transplantation
- There is a major violation of the clinical study protocol
- The development of any exclusion criteria that might jeopardize safety (see Section 8.3 , Exclusion Criteria)
- Pregnancy

Patients who choose to discontinue investigational product prior to termination of the study are expected to also continue to follow the regular visit schedule, with the exception of PK sampling, through to study closure.

Patients who undergo a liver transplant during the course of the study must discontinue investigational product and should complete early termination procedures, if possible.

The Investigator is encouraged to contact the Sponsor prior to discontinuing a patient from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any patient prematurely withdraws from the study.

8.4.1.1. Pregnancy

Whenever the site is notified of a possible pregnancy, the patient should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female patient becomes pregnant, the patient must stop taking investigational product immediately and be withdrawn from the study. The patient must be followed by the Investigator through pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor. For reporting purposes, pregnancy is not considered an AE (see Section 13.1.10).

8.4.2. Other Reasons for Discontinuation of Investigational Product or Study Termination

Subjects who discontinue investigational product are expected to continue in the study until the end of the study or at the discretion of the Sponsor. If a patient experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe.

Early termination procedures should only be conducted if the patient withdraws consent (See Section 9.7.14).

It is agreed that, for reasonable cause, either the Investigator or the Sponsor, may terminate this study.

The following events are considered appropriate reasons for a subject to discontinue from the study:

8.4.2.1. Withdrawal of Consent

If the patient decides that it is in his/her best interest to discontinue from the study, he or she may withdraw consent. It is fully understood that all patients volunteer for the study and that they may withdraw their consent to continue in the study at any time.

A reasonable effort must be made to determine the reason(s) for patient discontinuation. This information and date must be recorded in the appropriate eCRF.

8.4.2.2. Lost to Follow-Up

If a patient fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the patient, he or she will be withdrawn from the study.

A reasonable effort (ie two phone calls/messages, no response to registered letter) must be made to contact the patient and determine the reason(s) why a patient fails to return for a study visit or is lost to follow-up. This information and date of contact must be recorded in the appropriate eCRF.

8.4.2.3. Elevated Liver Enzymes

An increase in AST or ALT to >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN) should be followed by repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing. Adverse event information should also be collected. If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms. The Investigator should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable.

The Medical Monitor should be contacted, as appropriate.

8.4.3. Patient Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. Patients will be considered "lost to follow-up" only after reasonable, documented attempts to reach the patient prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a patient fails to return for required study visits or discontinues from the study. This information must be documented in the eCRF.

If a patient is withdrawn from the study early (regardless of the cause), all of the EOS/EOT/ early termination (ET) evaluations are to be performed at the time of withdrawal, to the extent possible.

9. TREATMENT OF PATIENTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or placebo.

Two treatment groups will be evaluated: OCA and placebo. Investigational product will be administered orally. Each dose will be made up of 1 tablet (ie, one OCA 5-mg tablet or one OCA 10-mg tablet, or matching placebo).

Investigational product will be taken orally with water for the duration of the study. Patients will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time on dosing days. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 8) during the study.

Concomitant medications (will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications (including prescribed, over the-counter, or herbal preparations) taken prior to (ie, within 30 days of Screening) and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 1 (ie no change in dosing within 3 months of screening).

PBC Specific Therapy

Investigators will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. Throughout the course of the study, Investigators are expected to monitor patients' PBC regimens and, if responsible for usual care, may adjust the regimen in order to achieve locally-appropriate treatment goals. These goals will be individualized, with the understanding that currently applicable PBC guidelines may vary among different geographic regions.

Ideally, patients should generally remain on the baseline PBC therapies throughout the course of the study, unless the baseline PBC therapy is no longer considered clinically appropriate by the Investigator. In addition, patients should be reminded to keep taking their blinded investigational product.

9.2.1. Drug Interactions

Patients taking bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (and UDCA; ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration).

OCA taken concomitantly with warfarin may result in decreased international normalized ratio (INR) levels, therefore, INR should be monitored and the dosage of warfarin adjusted, as needed during treatment with OCA and after cessation of OCA, to maintain the target INR range.

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate probe, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

Information related to additional drug-drug interaction studies is available in the current version of the IB. The aforementioned sections of the IB should be referred to during the course of the study, and are accessible to investigators to help facilitate the assessment of potential drug-drug interactions (DDI) with OCA that may be observed in study patients.

9.2.2. Prohibited Medications

Commercial OCA therapy (if available) is prohibited while on investigational product, and if prescribed during the course of the study, the Investigator should be cognizant of the possibility of double dosing. Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.2). Fibric acid derivatives (fibrates) and other medication intended to lower blood triglyceride levels are also prohibited while on investigational product.

9.3. Treatment Compliance

The Investigator should assess the patient's compliance with dosing of investigational product at each study visit, and confirm by conducting investigational product accountability (ie, count of returned tablets).

Patients should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the indicated visits (Table 1). The Investigator or designee should perform investigational product accountability (ie, count of returned tablets) and, if applicable, follow-up with the patient to retrieve any investigational product bottles that have not been returned.

If the Investigator has concerns about a patient's dosing compliance, he or she should discuss this with the patient, assess the reasons for noncompliance and the likelihood that the patient will remain noncompliant, and notify the Sponsor accordingly.

9.4. Randomization and Blinding

9.4.1. Methods of Assigning Patients to Treatment Groups

This study will be conducted in a double-blind, placebo-controlled manner. Enrolled patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: placebo or OCA based on a predefined randomization code (generated by Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based patient registration system at Screening and Day 1.

Randomization will be stratified by CP class (CP-B or CP-C). Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores. The IWRS will serve as the investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the patient in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the patient to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind.

9.4.2. Blinding

The patients, Investigator, and study site staff will be blinded to the patient's treatment allocation during the patient's participation in the double-blind phase of the study.

9.4.3. Emergency Unblinding Procedures

Treatment assignment for individual patients will be made available to the Investigator for medical emergency use only (such as unblinding which is necessary in order to treat an SAE) through the IWRS system. When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment assignment is necessary for further medical management of the patient). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the patient's record the rationale for unblinding and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment. Procedures for unblinding a patient's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual patient for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The DMC will have access to the IWRS and will be able to unblind individual patients. Refer to Section 15.8 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded patient data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the study is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DMC.

Access to treatment assignments will also be made available to the designated Intercept staff responsible for expedited safety reporting of suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

9.5. Assignment of Site and Patient Numbers

9.5.1. Site Numbers

Each study site selected to participate in this study will be assigned a site number by the Sponsor. The site number will be used to categorize patient data and to identify the site and/or Investigator within study documents. This number will be recorded in the eCRF.

9.5.2. Patient Numbers

Patients will be identified by a unique six-digit number, independent of the randomization number. The first three digits will represent the site number and the last three digits will represent the Screening number.

9.6. Restrictions

Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited.

9.6.1. Fasting Requirement at Study Visits

All patients must have been fasting for at least 8 hours prior to their Screening Visit and all subsequent study visits, as all analytes will be assayed in fasting blood or plasma samples. Water is permitted during the fasting period.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. For example, Week 6 should ideally occur 6 calendar weeks (± 7 days) following Day 1.

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies or on electronic devices such as iPads) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated consent form. Patients will also be provided a separate ICF before providing blood samples for genetic analysis and must be willing and able to provide consent as described above.

9.7.3. Assessing Cirrhosis

To determine which dosing regimen patients should follow, cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators:

- Biopsy results consistent with PBC Stage 4 (Ludwig 1978)
- Transient Elastography Median Value ≥16.9 kPa (Corpechot 2012)
- The presence of any of the following (unless exclusionary per Section 8.3) in the absence of acute liver failure:
  - Varices
  - Ascites
  - Radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
- Combined low platelet count (<140 000/mm^3) with:
  - persistent decrease in serum albumin, or

- elevation in prothrombin time /INR (not due to antithrombotic agent use), or
- elevated bilirubin (2× ULN)

Patients will be dosed according to their CP Score calculated in the eCRF (see Section 14.1.1 and Table 12).

Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in cirrhosis status will necessitate re-evaluation of the dosing regimen.

9.7.4. Screening Procedures (-1 day to 14 days prior to Day 1)

The Screening Visit assessments must be performed within ≤14 days prior to Day 1 to determine whether the patient meets all the inclusion criteria and none of the exclusion criteria. Patients who do not fulfill all eligibility criteria will not be enrolled in the study. Patients may be rescreened after 2 months have elapsed from the date of their most recent screening visit procedure; however, all Screening procedures (including obtaining informed consent) should be repeated and a new three-digit Screening number assigned.

Screening Visit procedures are as follows:

- The patient is to review and sign the ICF. Informed consent must be obtained from the patient before performing any study-related procedures, including Screening procedures.
- Collect medical history (including smoking and alcohol consumption history and current habits of both).
- PBC history
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Perform a standard 12-lead electrocardiogram (ECG).
- Perform assessments for calculation of CP Score (Section 14.1.1)
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Virology Screen (HCV and HBsAg)
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis (dipstick).
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test in females of childbearing potential.

- Provide kits and instructions for collection of stool specimens at home prior to the Day 1 visit
- Instruct the patient to fast overnight (at least 8 hours) before the next visit (water is permitted)

9.7.5. Day 1 Procedures (Randomization)

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Perform a physical examination.
- Review and record prior concomitant medications.
- Perform TE using the Fibroscan® TE device. If TE has been done within 3 months of Day 1 and a report/adequate data are available, a pretreatment TE at Day 1 is not required. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed.
- Perform assessments for calculation of CP Score (Section 14.1.1)
- Quality of Life and Patient questionnaires (Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant heath care professional (HCP) or non-HCP related office visits that have occurred since the previous study visit.
- Randomize the patient only if s/he meets all inclusion criteria and no exclusion criteria.
- Record the visit in IWRS and dispense investigational product
  - Instruct the patient to begin dosing on the day after the Day 1 visit. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation

  - Obtain blood samples for markers of inflammation
  - ELF (including HA, P3NP, and TIMP-1)
  - C4, and FGF-19, bile acids
  - Trough PK assessment
- Obtain urine sample for urinalysis (dipstick).
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted

9.7.6. Week 3 (Safety Contact)

Patients should be contacted by telephone at Week 3 to assess for AEs and verify that s/he is dosing as directed.

- Contact patient by phone/email.
- Review and record prior concomitant medications.
- Assess and record AEs.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.7. Week 6 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF

  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform a physical examination.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Quality of Life and Patient questionnaires (see Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Record the visit in IWRS and dispense investigational product
- Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - C4, and FGF-19, bile acids
  - Trough PK assessment
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.8. Week 12 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF

  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.

- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Perform a physical examination.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Quality of Life and Patient questionnaires (see Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess for dose titration, if eligible
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Record the visit in IWRS and dispense investigational product
- Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Obtain blood samples for markers of inflammation
  - ELF (including HA, P3NP, and TIMP-1)
  - C4, and FGF-19, bile acids
  - Trough PK assessment
- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hr post dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose

Note: Patients should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Patients should not drink any water until at least one hour post dose

- Assess the patient's supply of investigational product to ensure an adequate amount.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.9. Week 18 and Week 30 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform a physical examination.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Quality of Life and Patient questionnaires (see Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Record the visit in IWRS and dispense investigational product
- Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Obtain blood samples for

- Serum chemistry, hematology, and coagulation
- C4, and FGF-19, bile acids
- Trough PK assessment

- Serial PK assessment **will only be conducted in patients who are uptitrating to the next dose level**.
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hr post dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose

Note: Patients should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Patients should not drink any water until at least one hour post dose

- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.10. Weeks 24 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Perform a physical examination.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).

- Quality of Life and Patient questionnaires (see Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess for dose titration, if eligible.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Obtain blood samples for markers of inflammation
  - ELF (including HA, P3NP, and TIMP-1)
  - C4, and FGF-19, bile acids
  - Trough PK assessment
- Serial PK assessment; **will only be conducted in patients who are uptitrating to the next dose level**.
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hr post dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose

Note: Patients should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Patients should not drink any water until at least one hour post dose

- Perform TE using the Fibroscan® TE device.
- Assess the patient's supply of investigational product to ensure an adequate amount.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.11. Week 36 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Perform a physical examination.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Quality of Life and Patient questionnaires (see Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess for dose titration, if eligible
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Record the visit in IWRS and dispense investigational product
- Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Obtain blood samples for markers of inflammation
  - ELF (including HA, P3NP, and TIMP-1)
  - C4, and FGF-19, bile acids
  - Trough PK assessment
- Serial PK assessment; **will only be conducted in patients who are uptitrating to the next dose level**.
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose

- Immediately following 1 hr post dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
- Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose

Note: Patients should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Patients should not drink any water until at least one hour post dose

- Assess the patient's supply of investigational product to ensure an adequate amount.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.12. Week 48 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform a physical examination including smoking and alcohol consumption history and current habits for both.
- Perform 12-Lead ECG
- Perform TE using the Fibroscan® TE device.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Quality of Life and Patient questionnaires (see Section 13.2.6).
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Urinalysis (dipstick)
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for

  - Serum chemistry, hematology, and coagulation
  - Obtain blood samples for markers of inflammation
  - ELF (including HA, P3NP, and TIMP-1)
  - C4, and FGF-19, bile acids
  - Trough PK assessment
- Serial PK assessment; **will only be conducted in patients who are uptitrating to the next dose level**.
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hr post dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose

Note: Patients should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Patients should not drink any water until at least one hour post dose

- Perform TE where available using the Fibroscan® TE device.
- Schedule the follow-up visit and advise the patient:
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.13. Every 3 Months after Week 48

Patients who have completed their 48-week double-blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the primary treatment period and the database is locked. Assessments including a review of all AEs and safety laboratory results (eg, chemistry, hematology, and coagulation) will be done every 3 months as described in Section 9.7.7. Patients' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated CP Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments as described in Section 7.4 and should not exceed the indicated maximal dose and frequency indicated for their CP category. Patients will then have the option to continue into an open-label LTSE.

9.7.14. End of Treatment/Early Termination Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent

Patients who discontinue investigational product are expected to continue in the study until the end of the study (EOS) or at the discretion of the Sponsor.

EOT/ET procedures will be required whenever patients discontinue treatment with investigational product. The EOT/ET visit and procedures listed below must be performed as close as possible to the patient's last dose of investigational product. When a patient discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed as the patient's final study visit. The actual investigational product discontinuation scenario (Table 4) will determine the sequence of the EOT/ET and EOS visits and procedures. In some cases, the EOT/ET visit and procedures will precede the EOS visit; in others, the EOT/ET and EOS visits will be combined and performed as close as possible to the patient's last dose of investigational product.

When a patient ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (ET) (withdrawal of consent) or discontinuation, an EOT/EOS visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. The purpose of this visit is to conduct complete and/or final assessments on or as near as possible to the final day of dosing. In some cases, the patient may discontinue on the day of a scheduled study visit. In these cases, EOT/EOS visit procedures should be performed in place of the scheduled study visit procedures. The data will be recorded as EOT/ET and EOS procedures in the eCRF.

Table 4: Early Discontinuation Scenarios

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Early Termination	Discontinued	Withdrawn	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose of investigational product	Complete at final study visit
	Discontinued	Record review only	Record review only	Combined visit, completed as close as possible to last dose of investigational product	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product	
Pregnancy	Discontinued	Complete per the above scenarios - Early Termination or Treatment Discontinuation			
Treatment Interruption	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose of investigational product	Complete at final study visit
Lost to Follow-Up	Discontinued	LTF	None	Unable to complete due to LTF status	

EOS = end of study; EOT = end of treatment; LTF = lost to follow-up

[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the EOS and EOT Visits.

[b] Includes initiation of commercially available OCA

9.7.15. Unscheduled Safety Visit

The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted.

As appropriate, the Medical Monitor should be contacted.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

The investigational product is a white, round, film coated tablet containing OCA 5 mg or 10 mg or matching placebo. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

10.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to Good Manufacturing Practice standards by a designated qualified vendor. All investigational product will be provided as tablets for oral administration and provided in high density polyethylene bottles with heat induction seals and child resistant closures. The bottle packaging will not reveal any information about the treatment dose contained in the bottle. Multiple bottles may be dispensed to the patient at each visit to provide enough tablets for dosing until the next visit.

The designated investigational product packaging/distribution vendor will also be responsible for the distribution of the investigational product to the Investigator.

10.3. Investigational Product Storage

Investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.

10.4. Investigational Product Administration

Refer to Section 9.1.

10.5. Investigational Product Accountability and Disposal

The Sponsor's representative will send investigational product to the study site under appropriate storage conditions. All shipments of investigational product should be unpacked and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product against the shipment documentation. The pharmacist or designee should contact the Sponsor immediately to report any concerns regarding the shipment.

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of investigational product accountability, including records of individual patient dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the Clinical Research Associate (CRA), will review accountability records against investigational product dispensed and that remaining in stock, during on site monitoring visits and when the study is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the investigational product. If the investigational product is to be returned to the Sponsor's vendor for destruction, the CRA will also prepare the investigational product for shipment.

11. OVERVIEW OF ASSESSMENTS

The assessments supporting the objectives for the study are in Table 5:

Table 5: Table of Assessments

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates glyco-OCA, tauro-OCA, and OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus and fatigue
Secondary Objectives	**Assessments**
Changes in Risk Scores	Changes in MELD and CP Score components
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma, fecal bile acids
Additional Objectives	**Assessments**
Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30, and others as determined during course of study.
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	Transient Elastography and ELF (including HA, P3NP, and TIMP-1)
PK/PD relationship of OCA and liver biochemistry	OCA and its conjugates, glyco-OCA tauro-OCA; and OCA glucuronide
PK/PD relationship of OCA and bile acid homeostasis	Bile acids
Patient reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
PK/PD relationship of OCA: Markers of safety and tolerability	Pruritus and fatigue
Clinical outcomes	Incidence and time to first occurrence of any of the following: all-cause mortality, liver-related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, hepatocellular carcinoma

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; HDL = high density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IgA = immunoglobulin; A IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; MACE = Major Adverse Cardiovascular Events; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PD = pharmacodynamics; PK = pharmacokinetic; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; SAE = serious adverse event; TNF-α = tumor necrosis factor-α, VAS = visual analog scale

12. CLINICAL PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic analyses will be based on the PK population (Section 15.1). Subjects with at least one PD assessment after dosing will be included in the combined PK/PD analyses.

12.1. Pharmacokinetic Blood Sampling

Serial and trough PK assessments will be performed in all patients participating in the study.

At each visit, patients will provide fasted blood samples for measurement of OCA and its conjugates glyco-OCA, tauro-OCA, and OCA glucuronide 30 minutes before administration of investigational product (predose) (Table 6). Patients will then receive a dose of investigational product with approximately 240 mL of water.

Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. (see Table 7) on Week 12 and prior to uptitrating to the next dose level of OCA. PK assessments will be based on patient's current dosing regimen (ie, prior to uptitrating to the next dose level).

Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be provided following collection of the 1-hour PK sample; the meal will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 6-hour sample collection.

During the double-blind treatment period and double-blind LTSE:

- Pharmacokinetic trough samples will be obtained from all patients at all visits prior to dose administration in accordance with Table 7.
- Serial PK assessments will be performed in all patients at Week 12. Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible and uptitrated their dose. Sample collection for fecal analysis will occur concurrent with serial PK sampling visits only.

Table 6: Acceptable Windows for Pharmacokinetic Sample Collection

Nominal Sampling Time	Acceptable Sampling Window
Before administration of investigational product (predose or trough)	Within 30 minutes before dosing
0.5 to 1.5 hours after investigational product	± 10 minutes
2 to 2.5 hours after investigational product	± 20 minutes
3 to 6 hours after investigational product	± 30 minutes

Table 7: Pharmacokinetic Sampling Schedule

	Double-Blind Treatment Period, Day									
	Screening	**1**	**6**	**12**	**18**	**24**	**30**	**36**	**48**	**ET/EOT**
PK trough collection[a]		X	X	X	X	X	X	X	X	
PK serial collection and fecal analysis		To occur at Week 12 and any up-titration visit								

EOT = end of treatment; AT = early termination; PK = pharmacokinetic
[a] Pharmacokinetic trough samples will be obtained from all patients at all visits prior to dose administration.
[b] Serial PK assessments will be performed in all patients at Week 12. Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible and uptitrated their dose. Sample collection for fecal analysis will occur concurrent serial PK sampling visits only.

12.2. Processing and Handling of Pharmacokinetic Samples

Whole blood will be collected at each scheduled sample time point. Detailed procedures for the collection of blood samples including further processing into plasma will be provided in a separate laboratory manual. The storage and shipment procedures for subsequent bioanalysis, will be provided to the investigational site in a separate document before the study is initiated.

12.3. Bioanalysis

Plasma concentrations of OCA and its conjugates glyco-OCA, tauro-OCA, and OCA glucuronide will be determined using a GLP validated liquid-chromatography mass spectrometry/ mass spectrometry method. A detailed description of validation information and results from the bioanalytical assay will be provided in separate reports. These samples may be used for evaluation of metabolites of OCA or other concomitant medication, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by OCA. These data would only be used for exploratory purposes and may not be included in the clinical study report.

13. ASSESSMENT OF SAFETY

Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.

Safety will be assessed in terms of AEs. All AEs, whether observed by the investigator, reported by the patient, noted from laboratory findings, or identified by other means, will be recorded from the time the patient signs his/her consent form (s)until the patient completes study participation (final Follow Up Visit).

Recording AEs/SAEs in the electronic data capture (EDC) system is the method for reporting AEs/SAEs. It is therefore imperative, that AEs/SAEs are recorded into the EDC.

13.1. Adverse Events and Serious Adverse Events

13.1.1. Definitions of Adverse Events

13.1.1.1. Adverse Event

AEs are defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to investigational product. An AE, also referred to as an adverse experience, can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) patient deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE.

Patients should be questioned about AEs in a general way, without leading the patient or asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

13.1.1.2. Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

13.1.1.3. Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

13.1.2. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 8. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as suspected adverse reaction (SAR). "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "definite," "probable," or "possible" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 8: Relationship of Adverse Events to Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; that is confirmed by stopping or reducing the dosage of the investigational product; and that could not be reasonably explained by the known characteristics of the patient's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product; that does not follow a known or suspected response pattern to the suspected investigational product; and that could reasonably be explained by known characteristics of the patient's clinical state.
Not Related	Any event that does not meet the above criteria.

13.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, severe, life threatening, or death as defined in Table 9 must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 9: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
2 = Moderate	Minimal, local or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.
3 = Severe	Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.

13.1.3.1. Severity of Pruritus (as an Adverse Event)

To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used for AE reporting. As pruritus is a patientive symptom, clinical judgment should be used to determine its severity and management Table 10.

Table 10: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus and Medical Intervention
1 = Mild	Generally localized; causing no limitation of usual activities or minimal sleep disturbance; the patient may experience slight discomfort. Medicinal intervention is not indicated.
2 = Moderate	Intense or widespread; causing some limitation of usual activities or sleep disturbance; the patient may experience annoying discomfort. Medicinal intervention may be indicated.
3 = Severe	Intense or widespread and interfering with activities of daily living (ADL), ie, causing inability to carry out usual activities, or severe sleep disturbance; the patient may experience intolerable discomfort. Medicinal intervention is typically indicated.

13.1.4. Reporting of Adverse Events and Serious Adverse Events

13.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the patient fully completes her/his study participation of the study.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

13.1.4.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

All SAEs must be reported to the Sponsor (including suspected liver-related clinical outcome events that qualify as serious). SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by:

- E-mail to the SAE email address: PPD
- Fax using a paper SAE report form: PPD
- Telephone: PPD

If an SAE is reported by telephone or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Patient number
- Event term
- At least 1 criterion classifying the event as serious
- Name and title of the reporting individual
- Causal relationship to the investigational product

The Investigator will assess whether the event is causally related to the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of Safety Reports/Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to PPD or emailed to PPD as soon as possible.

The Investigator is responsible for submitting information on Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local country requirements. Documentation of the submissions to IRBs/IEC s must be retained in the appropriate study file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate investigative site study files or with the IB.

SAEs involving suspected liver-related clinical outcome events will be processed and reported by the Sponsor as described in Section 13.1.5.

13.1.5. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition (see Section 13.1.1.3) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 13.1.4.2). The Sponsor is responsible for regulatory reporting of SAEs, including expeditious reporting of SUSARs, which are defined as SAEs that are considered related (definitely, probably, or possibly related) to the investigational product and considered unexpected as defined in the IB.

The Sponsor will consider the following list of clinical outcome events Medical Dictionary for Regulatory Activities (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a non-expeditious manner: death, end-stage liver disease (preferred term: chronic hepatic failure), liver transplant (preferred term: liver transplant), HCC (preferred term: hepatocellular carcinoma), variceal bleeding (preferred term: gastroesophageal variceal haemorrhage), ascites (preferred term: ascites), hepatic encephalopathy (preferred term: hepatic encephalopathy), and spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).

13.1.5.1. Potential Clinical Outcome Events

The events listed below will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events. These events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.

Potential Clinical Outcome Events:

Hospitalization for clinical complications of cirrhosis.

Given that the Potential Clinical Outcome Events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously report suspected Potential Clinical Outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a "potential study event" on the Adverse Event eCRF and will be submitted for adjudication to the Adjudication Committee as described in Section 15.9.

13.1.6. Additional Investigator Responsibilities for SAEs

The safety data recorded in the EDC represent the official record of all AEs and SAEs reported in the study. The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the patient's AE EDC. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Sponsor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for patient care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the Medical Monitor.

13.1.7. Notification of Post-Study SAEs

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2.

13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study

Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

13.1.9. Follow-Up of AEs and SAEs

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final visit that are deemed to be 'possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented on the eCRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

All patients showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

13.1.10. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's learning of the pregnancy by completing.

In the situation that the EDC is not functioning, the Medical Monitor should be notified by telephone. The investigator remains responsible for entering the pregnancy information into the EDC when the EDC becomes functional.

Completing the pregnancy report in the EDC is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 13.1.4 must also be followed.

13.2. Other Safety Parameters

13.2.1. Medical History/Demographics

A complete medical history will be obtained from the patient at screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

13.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the visits specified in the Schedule of Study Procedures (Table 1). A basic physical examination should be performed, including all body systems pertinent to the patient. Any clinically significant abnormality should be reported on the AE eCRF page for findings that appear after consent, and on the medical history eCRF for any finding present prior to consent.

13.2.3. Vital Signs

Vital signs will be assessed at indicated visits: oral temperature, sitting heart rate, respiratory rate and sitting blood pressure (BP). When taking heart rate, respiratory rate and BP readings, patients should be seated quietly for a minimum of 3 minutes before the readings are taken.

13.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after Day 1 will also be documented as AEs and entered on the AE page of the eCRF.

Investigative sites must retain a copy of all 12-lead ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date and time.

13.2.5. Laboratory Assessments

Except for Screening, patients will be instructed to attend each study visit in a fasted state, preferably in the morning, and patients should remain fasted until their blood samples have been collected. For visits that require fasting, the Investigator or designee will verify that the patient has fasted for at least 8 hours and record fasting status in the source and eCRF. If the patient reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and eCRF and remind the patient that fasting is required before all study visits.

Blood samples for serum chemistry, coagulation, and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (see Table 1). The number and volume of samples to be collected at each visit will be detailed in the laboratory manual.

Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a separate procedural manual. All necessary collection supplies will be

provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

All patients with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.

Laboratory samples will be stored for a maximum of up to 1 year after the end of the study (depending on stability) in the event that retesting is required, and destroyed after 1 year if not analyzed.

The list of laboratory analytes to be tested is shown in Table 11.

Table 11: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen, creatinine, direct bilirubin, total bilirubin, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)
Coagulation	PT, PTT, INR
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive), dipstick
Biomarkers of Hepatic Fibrosis and/or Inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30, and others as determined during course of study.
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	HA, P3NP, and TIMP-1
Genetics	DNA including single-nucleotide polymorphisms that may be involved in PBC; RNA
Other	OCA (parent and conjugates [glyco and tauro], OCA-glucuronide) and C4

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope M30; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; HDL = high density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-6 = Interleukin 6; INR = international normalized ratio; LGL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; OCA = obeticholic acid; PBC = primary biliary cirrhosis; P3NP = procollagen 3 N-terminal peptide; PT = Prothrombin time; PTT = partial thromboplastin time; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TG = triglyceride; TIMP-1 = tissue inhibitor of metalloproteinase 1; TNF-α = tumor necrosis factor-α, VLDL = very-low density lipoprotein

Urine based β-hCG pregnancy tests will be performed in female patients of childbearing potential per protocol specified visits (see Table 1). If a urine pregnancy test is positive, a serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified and the patient will be followed as outlined in Section 13.1.10 until pregnancy outcome.

International normalized ratio (INR) will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, Na, and INR values, with modification by United Network for Organ Sharing. Total OCA will be calculated based on OCA, tauro-OCA, glyco-OCA, and OCA glucuronide concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.

13.2.6. Patient-Reported Outcomes and Healthcare Resource Use

Data will be collected to determine the effects of OCA on health-related quality of life. Healthcare resource use as well as a general health status assessment (for the purposes of generating health utilities) will be used to support subsequent cost-effectiveness analyses that are relevant to major health care systems around the world. Assessments of patient-reported outcomes will take place during the visits indicated in Table 1.

The following patient-reported outcomes will be used to evaluate the effects of OCA compared to placebo on improvements in health-related quality of life:

- PBC-40: The PBC-40 is a validated disease-specific 40-question quality of life questionnaire, which consists of 6 domains: General Symptoms, Itch, Fatigue, Cognitive Function, Social, and Emotional (Jacoby 2005).
- EQ-5D-5L: The EQ-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VASs). The descriptive system is organized into 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the patient's self-rated health on a 20-cm vertical, line with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman 2011, Oemar 2013).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual patients.
- Chronic Liver Disease Questionnaire (CLDQ): The CLDQ is a disease-specific health related quality of life questionnaire for patients with chronic liver disease. The questionnaire includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry). Each question is answered on a scale from 1 (always) to 7 (never) with a higher score corresponding to a better quality of life. The CLDQ produces a summary score and domain scores that correlate with the severity of liver disease (Younossi 1999).

Patients will be asked to complete the questionnaires and initial and date each document. The questionnaires should be filed in the patient's study records. These may require transcription to the eCRF by study site staff.

Healthcare resource use will be collected from eCRFs including number, reason for and duration of hospitalizations and emergency room visits, number of outpatient physician visits (patient reported), and use of concomitant medications. The purpose is to evaluate the effects of OCA compared to placebo on patient-reported outcomes and healthcare resource.

14. EFFICACY ASSESSMENTS

14.1.1. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory. Investigators will be responsible for determining the appropriate dosing regimen based on the CP score (Table 1 and Table 12). Any change in CP Score will necessitate re-evaluation of the dosing regimen.

Table 12: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	µmol/L	<35	35-50	>50
	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	28-35	<28
	g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Mild	Moderate-Severe
Hepatic encephalopathy[a]		No	Grade 1 or 2	Grade 3 or 4

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
(Pugh 1973, Lucey 1997)

14.1.2. Model of End Stage Liver Disease Score

The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is useful in assessing patients with significant decompensation and the MELD score is now

used by the United Network for Organ Sharing in the US and Eurotransplants to manage the organ allocation for liver transplantation. The threshold for placement on an organ transplantation queue varies between regions across the globe but a score of 15 results in a place on the transplant waiting list in the US.

An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival and is calculated according to the following formula:

MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43

MELD score will be calculated and reported in whole numbers according to the frequency listed in Table 1.

14.1.3. Changes in Liver Biochemistry and Hepatobiliary Damage

ALP, ALT, AST, GGT, total and direct bilirubin, INR, creatinine, albumin, platelets will be measured according to the frequency listed in Table 1.

14.2. Additional Assessments

14.2.1. Markers of Inflammation, Apoptosis and Necrosis

Blood samples for analytes including hs-CRP, IgM, TNF-α, and cytokeratin-18 neoepitope M30. Assessments will be performed according to the schedules presented Table 1.

14.2.2. Noninvasive Measurements of Liver Stiffness and Fibrosis

The ELF test assesses: HA, P3NP, and TIMP-1. Samples will be assessed in patients according to the schedules presented in Table 1.

The Fibroscan® TE device (Echosens, Paris, France) will be used at all study sites that have the equipment to collect hepatic stiffness measurements. These study sites must have the staff trained in the use and data interpretation of the device. This is a validated and non-invasive technique used to assess hepatic fibrosis which will be conducted according to according to the schedule presented in Table 1.

14.2.3. Markers of FXR activation

Blood samples will be collected in all patients to measure C4, FGF-19, and bile acids. The results of these analyses will be used to assess the PK/PD response of OCA. Blood samples will be assessed in patients according to the schedule presented in see Table 1.

14.2.4. Potential Clinical Outcome Events

Potential clinical outcome events will be evaluated by an Adjudication Committee (described in Section 15.8) to confirm if they meet the criteria to be considered Clinical Outcome Events.

Given that the Potential Clinical Outcome Events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously

report suspected Potential Clinical Outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a "potential study event" on the Adverse Event eCRF and will be submitted for adjudication to the Adjudication Committee as described in Section 15.8

15. STATISTICAL METHODS AND ANALYSES

Individual subject data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by subject. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on treatment study days are numbered relative to the day of the first dose of investigational product which is designated as Day 1.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, Baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For continuous variables, the number of subjects, mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more decimal place than the raw data, and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations.

There will be no formal hypothesis testing in this study. However, summary statistics for each treatment group will be presented, as well as 95% CIs for the difference between the treatment groups.

15.1. Analysis Populations

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.

- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

15.2. Determination of Sample Size

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients per OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. The assessment was based on 80% powering for the 90% confidence interval of the geometric mean ratio of Total OCA (sum of OCA, glyco OCA, and tauro OCA).

15.3. Pharmacokinetic Analyses

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

PK analysis will based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.

15.4. Safety Analyses

Safety analyses will be conducted using the Safety population. Safety data, including AEs, vitals, ECG, and clinical laboratory results will be summarized by treatment group using the Safety Population.

The incidence of TEAEs and SAEs will be tabulated by system organ class and preferred term for each treatment group, and similarly by severity and relationship to treatment.

Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized.

CP scores will be summarized by treatment group at Baseline and at each post-Baseline visit.

No inferential comparison of safety endpoints will be performed. All safety comparisons will be descriptive.

15.4.1. Adverse Events

AEs will be coded using MedDRA. Summary tables of TEAEs will be provided.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs
- Subject incidence of TEAEs and the total number of entries by MedDRA SOC and PT. This summary will be repeated for all subgroups
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA SOC, PT, and closest relationship to investigational product (Related/Not Related). Related AEs are those with relationships reported as "Definite," "Probable," or "Possible," and unrelated AEs are those with relationships reported as "Unlikely" or "Not Related." At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and the total number of entries by MedDRA SOC and PT.
- Subject incidence of TEAEs leading to investigational product withdrawal or study discontinuation by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Subject Discontinued from Study" is checked.

The following listings will be presented by treatment group and subject:

- All adverse events.
- Serious adverse events (This is a subset of the AEs where serious is marked as "Yes").
- Severe adverse events (This is a subset of AEs where severity is marked as "Severe").
- Related adverse events (This is a subset of the AEs where relationship marked as "Definite," "Probable," or "Possible").
- Adverse events leading to Study Drug Withdrawal or Study Discontinuation (This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Subject Discontinued from Study" is checked).
- Adverse events leading to death (This is a subset of the AEs where the corresponding AE number is specified on the Death eCRF).

15.4.2. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.

Vital Signs

The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.

Electrocardiograms

Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.

15.4.3. Adverse Events of Special Interest

Pruritus: Treatment-emergent pruritus, defined as any preferred term including "Prur," will be summarized separately by the MedDRA SOC, treatment group, and PT as a subset of all TEAEs. This summary will be repeated for subjects with "new or worsened" pruritus events, as defined as follows:

- Mild, moderate, or severe treatment-emergent pruritus events in subjects with no pruritus at Baseline, or
- Worsening of the severity of the Baseline condition in subjects with pruritus at Baseline.

Baseline pruritus is defined as the investigator's rating of severity as collected on the PBC Disease History eCRF. Subjects whose Baseline severity is severe will be counted as worsening if an AE of pruritus with severe is recorded.

An analysis of treatment-emergent pruritus event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between pruritus and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent pruritus
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Subjects who never reported an AE of pruritus will be censored at the date of last contact.

- Time to onset of the first moderate or severe treatment-emergent pruritus
  - The time to the start of the first moderate or severe pruritus will be calculated by date of onset of the first moderate or severe pruritus – date of first dose of investigational product +1.
  - Subjects who never reported a moderate or severe AE of pruritus will be censored at the date of completion or discontinuation.
- Time to onset of the first severe treatment-emergent pruritus
  - The time to the start of the first severe pruritus will be calculated by date of onset of the first severe pruritus – date of first dose of investigational product +1.
  - Subjects who never reported a severe AE of pruritus will be censored at the date of completion or discontinuation.

The analysis of time to first onset of treatment-emergent pruritus AE, time to onset of the first moderate or severe treatment-emergent pruritus and onset of the first severe treatment-emergent pruritus will include the number of subjects with pruritus (first onset, first moderate or severe, first severe), the number of subjects without pruritus (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group.

Fatigue: Treatment-emergent fatigue is defined as any preferred term which includes "Fatigue." New or worsened treatment-emergent fatigue is defined as follows:

- Any mild, moderate, or severe treatment-emergent fatigue events in subjects with no fatigue at Baseline, or
- Worsening of the severity of the Baseline condition in subjects with fatigue at Baseline.

Baseline fatigue is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Subjects whose Baseline severity is severe will be counted as worsening if an AE of fatigue with severe is recorded.

An analysis of treatment-emergent fatigue event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between fatigue and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent fatigue
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Subjects who never reported an AE of fatigue will be censored at the date of last contact.

- Time to onset of the first moderate or severe treatment-emergent fatigue
  - The time to the start of the first moderate or severe fatigue will be calculated by date of onset of the first moderate or severe fatigue – date of first dose of investigational product +1.
  - Subjects who never reported a moderate or severe AE of fatigue will be censored at the date of last contact.
- Time to onset of the first severe treatment-emergent fatigue
  - The time to the start of the first severe fatigue will be calculated by date of onset of the first severe fatigue – date of first dose of investigational product +1.
  - Subjects who never reported a severe AE of fatigue will be censored at the data of last contact.

The analysis of time to first onset of treatment-emergent fatigue AE, time to onset of the first moderate or severe treatment-emergent fatigue and onset of the first severe treatment-emergent fatigue will include the number of subjects with pruritus (first onset, first moderate or severe, first severe), the number of subjects without fatigue (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group.

15.5. Efficacy Analyses

This study does not plan to test a formal hypothesis for any efficacy endpoint.

The endpoints of efficacy assessments are change in bilirubin, INR, creatinine, albumin, platelets, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Summary statistics of the laboratory values will be provided by treatment group. The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 95% CI of the difference will also be presented. No formal hypothesis testing will be performed.

Risk Scores: Changes from baseline in the MELD score and in CP score will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the

median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.

Shifts in MELD scores from Baseline will be reported by visit using the following categories: <10, 10 to <12, 12 to <13, 13 to <14, 14 to <15, and ≥15.

Child-Pugh class will be presented in shift tables showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of subjects within each shift classification.

Individual factors will be presented in a listing.

15.6. Additional Efficacy Analyses

Analyses of changes in liver stiffness and ELF, cytokeratin-and TIMP-1, and markers of inflammation will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin.

The following clinical outcomes will be captured in the study:

- All-cause mortality
- Liver related death
- Liver transplant
- Variceal bleed
- Hepatic encephalopathy
- Bacterial peritonitis
- Ascites
- Hepatocellular carcinoma

The incidence and time to first occurrence of any of the above listed clinical outcomes will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians and corresponding 95% CIs, if the medians can be estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the time to each of the above outcomes will be summarized by treatment group using the same methods as defined above.

15.7. Handling of Missing Data

Missing data will be assumed to be missing at random. No data will be imputed.

15.8. Data Monitoring Committee

An independent DMC that includes hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), and statistician(s) not involved in the study as Investigators, adjudication committee members, or consultants. The DMC will have oversight over the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the Food and Drug Administration (FDA) debarment list will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data in order to ensure the safe and proper treatment of patients. Based on review of these data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study.

Written minutes of both the open and closed DMC sessions will be prepared. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked.

Data listings provided to the DMC do not contain individual patient treatment information; however, the DMC will have access to the database and may unblind individual patient data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all patients and separate treatment columns with 'dummy' labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.

The DMC may agree to adjust meeting frequency based upon actual and projected safety and efficacy data availability. Adjustments to or stopping of the protocol defined doses may be considered based on DMC evaluation of OCA safety and tolerability.

All Investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to patient safety, which alter the conduct of this study. The Investigators will inform the patients of such actions and the protocol, PIS, and ICF will be revised, as appropriate.

15.9. Adjudication Committees

All suspected liver-related clinical outcomes, major adverse cardiovascular events (MACE)/expanded MACE, and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 3 committees and event types they are responsible for adjudicating are as follows:

- Cardiovascular Adjudication Committee (CAC): Adjudicates all suspected MACE, including all deaths

- Hepatic Outcomes Committee: Adjudicates all deaths and suspected liver-related outcomes
- Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events

Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the suspected events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual patient treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

Study records at each site will be monitored at regular intervals by a representative of the Sponsor, the CRA. The role of the CRA is to aid the Investigator in the maintenance and documentation of complete, accurate, legible, well organized and easily retrievable data. In addition, the CRA will ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such must be given access to the patient’s primary source documentation (eg, paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

The Investigator may exercise judgment in allowing the CRA access to particular sections of the patient's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

16.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IEC/IRB and/or regulatory agencies to conduct one or more site audits during or after the study and agrees to allow access to all study related documentation and information and be available for discussion about the study.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the Sponsor or designated personnel (eg, CRA), instruction manuals, data verification, cross checking and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate collection of study data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the PIS-IC and/or other patient information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to Intercept before he or she can enroll any patient into the study. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to study patients to the IRB/IEC for review.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. A favorable opinion on amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/ IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of SARs will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or its designee will provide reports to the IRB/IEC as requested, as a minimum annually, and after the study is complete.

18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

18.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated consent form must be obtained before conducting any study procedures.

18.4. Patient Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

The Investigator will maintain a list of patient's names and identifying information (eg, patient's hospital number, unique patient number). This list will not be collected by the Sponsor.

The PIS will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique patient number/randomization code/site number, only.

When personal data on patients are stored or processed by computer, the data must be protected to prevent disclosure to unauthorized third parties. The pertinent sections of the data protection laws in the country in which the protocol is being conducted will be complied with in full.

The PIS-IC will explain that, for data verification purposes, authorized representatives of the Sponsor, regulatory authorities, or IEC/IRBs may require direct access to parts of the hospital or study site records relevant to the study, including patient's medical history.

19. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the patients for the duration of the study. If the Investigator is not present in the study site during the assessment, he or she will leave instructions for the study site staff and a telephone number where he or she can be reached.

Named physician(s) will be responsible for the medical follow-up of patients, as applicable.

19.1. Adverse Event Reporting

The Investigator is responsible for recording AEs reported by the patient or discovered by any other means during the study. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

19.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the Investigator considers a patient's safety to be compromised if immediate action is not taken.

19.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

- Approved PIS-IC (all versions)
- IRB/IEC approvals (of protocol/amendments, patient questionnaires, etc)
- Form FDA 1572
- Current medical license of Investigators
- Curriculum vitae of Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

19.4. Ethics Review (IRB/IEC)

Please see Section 18.1 for the Investigator's responsibilities regarding ethics review.

19.5. Archiving and Record Retention

The Investigator should retain all correspondence relating to this study in the Investigator Site File (ISF). Any study documents stored elsewhere should have their location referenced in the ISF.

All documents relating to the study including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed study patient log and confidential patient identification list will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In the event that storage of records

becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor before the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

20. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include the following:

- Clinical Trial Registries (eg, www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (eg, basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions prior to the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data prior to the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.
- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance

with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.

- Single Center Publication and Additional Publications: This is a multicenter study and is designed to be published with complete data from all the study sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter study and that the study was not intended, or statistically powered, for data presentation by a single study site.
- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this study to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and amendments, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

21. LIST OF REFERENCES

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Corpechot C, Carrat F, Poujol-Robert A, et al. Noninvasive elastography-based assessment of liver fibrosis progression and prognosis in primary biliary cirrhosis. Hepatology. 2012;56(1):198-208.

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Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9.

Younossi ZM, Guyatt G, Kiwi M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic disease. Gut. 1999;45:295-300.

APPENDIX A. LIST OF STUDY 747-401 OUTCOME EVENTS

Some of the specified clinical endpoints will also by definition (see Section 13.1) qualify as Serious Adverse Events (SAEs). The sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 13.1.4). The Sponsor is responsible for regulatory reporting of SAEs including expeditious reporting of SAEs that are considered related to the investigational product and considered Unexpected by regulatory standards as defined in the Investigational Brochure.

The Sponsor may consider the following lists of events to be exempt from expeditious regulatory reporting but will continue to report them in a non-expeditious manner:

Potential Clinical Outcome Events:

Liver-related events resulting in death

Hepatic failure leading to liver transplant

Variceal bleed

Hepatic encephalopathy

Spontaneous bacterial peritonitis

Ascites

Hepatocellular carcinoma

Clinical Study Protocol 747-401

OBETICHOLIC ACID (OCA)

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

Version 2: 22 May 2017

EudraCT Number: 2017-001762-13

Sponsor

Intercept Pharmaceuticals, Inc.
4760 Eastgate Mall
San Diego, CA 92121
USA

TEL: PPD

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD , PhD

22 May 2017

Date

Vice President, Clinical Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-401. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected patients according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-401 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human patients in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

Medical Monitor

Primary Contact:	PPD MD Medical Director, Pharmacovigilance, Intercept Pharmaceuticals, Inc. (Intercept)
Telephone:	PPD
Email:	PPD
SAE Fax:	PPD
SAE Email:	PPD

2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; (6-ECDCA)

Title of Study:

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

Investigators and/or Study Center(s):

The study is planned to have approximately 35 investigational sites, globally.

Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment.	**Phase of Development:** Phase 4

Objectives:

Primary Objective:

- To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

Secondary Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - The model of end stage liver disease (MELD) score and its components
  - Child-Pugh (CP) score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

Additional Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - Markers of inflammation
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD Parameters and Safety and Tolerability assessments

- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ])
- To assess clinical events consistent with end-stage liver disease
  - Death (all-cause)
  - Liver transplant
  - Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)
  - 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
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

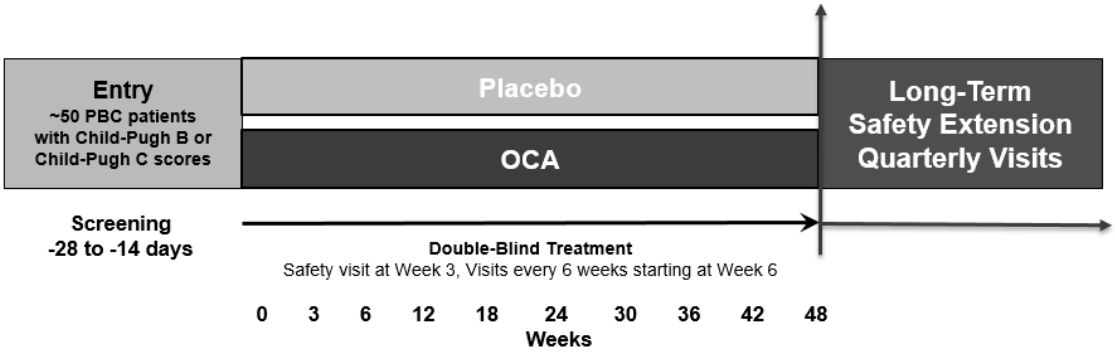
Methodology: This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with primary biliary cholangitis (PBC) and moderate to severe hepatic impairment defined as Child-Pugh B (CP-B) (moderate) and Child-Pugh C (CP-C) (severe) including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. At each visit (except screening and Week 3), fasting PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12, 18, 24, 30, and 48.

Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. Patients will then be given the option to go on open-label treatment.

Study Design Diagram



OCA = obeticholic acid, PBC = primary biliary cholangitis

Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score.

Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

Dosing Regimen:

All patients will initiate investigational product once weekly with 5 mg OCA or matching placebo. Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on safety and tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.

Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.

Patients with CP-C may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score

	Child-Pugh B (Moderate Hepatic Impairment)		**Child-Pugh C (Severe Hepatic Impairment)**	
	Treatment Group		**Treatment Group**	
	OCA	Placebo	OCA	Placebo
Starting Dose (Day 1)	5 mg once weekly	matching placebo	5 mg once weekly	matching placebo
Titration 1[a]	5 mg twice weekly[b]	matching placebo	5 mg twice weekly[b]	matching placebo
Titration 2[a]	10 mg twice weekly[b]	matching placebo	10 mg twice weekly[b]	matching placebo
Titration 3[a]	5 mg once daily	matching placebo	NA	NA

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Over the course of the study, a patient's CP category may change. When a patient demonstrates a change in CP category, dosing should be reassessed and modified if appropriate. Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply. If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen should be followed.

Maximum Dose for OCA or Matching Placebo for Changes in Child-Pugh Category

Original Status	**New Status**[a]		
	Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Child-Pugh B	*No change*	*No change*	10 mg twice weekly[b]
Child-Pugh C	5 mg once daily	5 mg once daily	*No change*

[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for the planned dosing regimen.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Number of Patients (planned): Approximately 50 patients will be enrolled in this study.

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines, defined as having ≥2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
    - Liver biopsy consistent with PBC (collected at any time prior to Screening)
2. Evidence of cirrhosis including at least one of the following:
    - Biopsy results consistent with PBC Stage 4
    - Liver stiffness as assessed by TE Median Value ≥16.9kPa
    - Clinical evidence in the absence of acute liver failure consistent with cirrhosis including: gastroesophageal varices, ascites, radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
    - Combined low platelet count (<140 000/mm^3) with
        - persistent decrease in serum albumin, or
        - elevation in prothrombin time/INR (not due to antithrombotic agent use), or
        - elevated bilirubin (2× ULN)
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening (ie, within 14 days before the first dose of investigational product):
    - Moderate: CP-B (Scores 7 to 9) or
    - Severe: CP-C (Scores 10 to12)
4. MELD score of 6 to 24 at Screening
5. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate or unresponsive to UDCA (no UDCA for ≥3 months)

Key Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. Hepatic encephalopathy (as defined by a West Haven score of ≥2)
5. History or presence of other concomitant liver diseases including:
    - Hepatitis C virus infection and RNA positive
    - Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B antigen negative) may be included in this study after consultation with the medical monitor
    - Primary sclerosing cholangitis
    - Alcoholic liver disease
    - Definite autoimmune liver disease or overlap hepatitis
    - Gilbert's Syndrome

6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function prior to randomization

Investigational Product, Dosage and Mode of Administration:

OCA 5 mg or OCA 10 mg tablets, oral administration

Placebo tablets, matched in size and appearance to OCA tablets, oral administration

Duration of Treatment:

Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment.

Criteria for Evaluation:

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus, and fatigue
Secondary Objectives	**Assessments**
Changes in risk scores	Changes in MELD and in CP score and components of the CP score
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma bile acids
Additional Objectives	**Assessments**
Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	TE and ELF (HA, P3NP, and TIMP-1)
PK/PD relationship	PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)
Patient-reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
Clinical events	Death (all-cause and liver-related), liver transplant, Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline), Hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, Uncontrolled ascites, and HCC.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope-M30; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; hs-CRP = high-sensitivity C-reactive protein; IgA = immunoglobulin; A IgG = immunoglobulin G; IgM = immunoglobulin M; IL-6 = interleukin 6; INR = international normalized ratio; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PBC = Primary Biliary Cholangitis; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TE = Transient Elastography; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; TNF-α = tumor necrosis factor; VAS = visual analog scale

Statistical Methods:

Analysis Populations:

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK Population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

Pharmacokinetic Analyses:

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, metabolite OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.

Safety Analyses:

Safety analyses will be conducted using the Safety population. Safety data, including AEs, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group. The incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs) will be tabulated by system organ class and preferred term for each treatment group, and similarly by severity and relationship to treatment. Laboratory parameters, physical examinations including vital signs, and electrocardiograms will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.

Efficacy Analyses:

This study does not plan to conduct a formal hypothesis testing for any efficacy endpoint.

The endpoints of efficacy assessments are change in total and direct bilirubin, INR, creatinine, albumin, platelets, ALP, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline values as covariates. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Additional Efficacy Analyses

Analyses of changes in liver stiffness and ELF, cytokeratin-and TIMP-1, and markers of inflammation will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.

The following endpoints consistent with end-stage liver disease will be captured in the study:

- Time to death (all cause)
- Time to liver-related death
- Time to liver transplant
- Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Time to variceal bleed

- Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)
- Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)

- Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

The incidence and time to first occurrence of any of the above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of HCC will be summarized by treatment group using the same methods as defined above.

Sample Size Justification:

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
6-ECDCA	6α-ethyl chenodeoxycholic acid (also known as INT-747)
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
BP	blood pressure
C4	7α-hydroxy-4-cholesten-3-one
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CK-18-M30	cytokeratin-18 neoepitope M30
CLDQ	Chronic Liver Disease Questionnaire
CRA	Clinical Research Associate
CP	Child Pugh
eCRF	electronic case report form
HCC	hepatocellular carcinoma
Hs-CRP	high sensitivity C-reactive protein
CP	Child-Pugh
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
ET	Early termination
FDA	Food and Drug Administration

Abbreviation or Specialist Term	Explanation
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid
HCC	hepatocellular carcinoma
HCP	Health care professional
HDLc	high density lipoprotein
IB	Investigational Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
ITT	intent-to-treat
IWRS	interactive web response system
KM	Kaplan-Meier
LDLc	low density lipoprotein
LTSE	Long-term safety extension
LS	Least squares
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model of end stage liver disease
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS-IC	patient information sheet/informed consent
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction

Abbreviation or Specialist Term	Explanation
SD	standard deviation
SEM	standard error of the mean
SI	standard international system of units
SOC	System organ class
SUSAR	suspected unexpected serious adverse reaction
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
the Sponsor	Intercept Pharmaceuticals, Inc.
TNF-α	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States (of America)
VAS	Visual Analogue Scale
VLDL	very low density lipoprotein

5. INTRODUCTION

5.1. Overview of Disease State and OCA

Primary biliary cholangitis (PBC, also known as primary biliary cirrhosis [Beuers 2015a, Beuers 2015b, Beuers 2015c]) is a serious, life-threatening, cholestatic liver disease of unknown etiology that, without treatment, frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and necessitates liver transplantation or results in death. PBC is a rare disease with reported prevalence in the US of 40.2/100 000 (Kim 2000). PBC disproportionately affects women approximately 10:1 and is typically diagnosed in patients between 40 to 70 years of age.

Historically, the only approved drug therapy for PBC has been the bile acid, ursodeoxycholic acid (UDCA), a physiological constituent of human bile (Lindor 2009). While UDCA therapy had a marked effect on the treatment of PBC, up to 50% of patients showed a suboptimal response or no response to UDCA. Such patients were at significantly increased risk of a poor clinical outcome due to PBC disease progression.

Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist and modified bile acid derived from the primary human bile acid chenodeoxycholic acid (CDCA) (Pellicciari 2002), was developed for the treatment of PBC and to provide patients who have an inadequate response to or poor tolerance of UDCA a novel treatment option that was safe and effective. In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication.

5.2. Nonclinical Experience with Obeticholic Acid

Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.

5.3. Clinical Development of Obeticholic Acid

As of 31 Jan 2017, approximately 2186 patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 525 patients had PBC, 686 patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, 52 patients had primary sclerosing cholangitis (PSC), and 5 patients had biliary atresia.

Overall, the pharmacokinetic (PK) profile of OCA is consistent with that expected of a bile acid. Phase 1 studies demonstrated that OCA is rapidly absorbed and extensively conjugated with glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates are primarily eliminated via biliary excretion, and plasma concentration time profiles demonstrated multiple peaking with prolonged exposure, indicative of enterohepatic circulation.

Plasma concentrations of OCA and its conjugates spike shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.

The OCA clinical development PBC program was based on a wide range of studies in PBC patients and healthy volunteers. The clinical pharmacology studies supported the proposed dosing regimen: 10 mg fixed dose and a titration regimen starting at OCA 5 mg with titration to 10 mg based on clinical and biochemical response. The clinical program included a pivotal Phase 3 clinical study (747-301) and two Phase 2 clinical studies (747-201 and 747-202), which formed the primary basis of approval of OCA.

Study 747-201 (59 patients) evaluated 2 doses of OCA (10 mg and 50 mg) given as monotherapy versus placebo. Statistically significant and clinically relevant relative and absolute reductions from Baseline in alkaline phosphatase (ALP) were achieved with both doses of OCA versus placebo ($p < 0.0001$). Mean relative ALP reductions were 45% (OCA 10 mg) and 38% (OCA 50 mg) compared to an increase of 0.4% with placebo. Further, significant improvements in gamma-glutamyl transferase (GGT) and in conjugated bilirubin were observed with both doses compared with placebo ($p < 0.05$). OCA also resulted in decreased circulating alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Study 747-202 (165 patients) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in patients on a stable therapeutic dose of UDCA. Overall, the data from 747-202 were consistent with Study 747-201. Statistically significant and clinically meaningful relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p < 0.0001$). Mean ALP reductions from baseline ranged from 21% to 25% compared to 3% with placebo. Improvements were also seen in GGT and ALT levels and in conjugated bilirubin levels.

Study 747-301 (216 patients) was a Phase 3, double-blind, placebo-controlled, parallel-group study followed by a long-term safety extension (LTSE) using OCA in patients with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of patients reaching specific criteria for ALP and bilirubin (ALP <1.67x upper limit of normal [ULN] with a ≥15% reduction and bilirubin ≤ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to <1.67x ULN with a ≥15% reduction from baseline and a normal bilirubin level after 12 months of therapy. The placebo group experienced a least squares (LS) mean decrease in ALP from baseline of 5%, compared to a significant LS mean decrease of 39% in the OCA 10 mg dose group and 33% in the OCA titration group (both OCA dose groups $p < 0.0001$ versus placebo).

The LTSE phases of both Phase 2 studies and the pivotal Phase 3 study support the long-term safety of OCA and demonstrate a durable therapeutic response.

Study 747-302 is an ongoing randomized, double-blind, placebo-controlled clinical outcomes study, designed to confirm the clinical benefit of OCA treatment in patients with PBC. This study is inclusive of patients with early to advanced stage PBC.

5.4. Rationale for Study Design and Dose for Investigational Product

5.4.1. Rationale for Study Design

There are limited clinical data available to support the use of OCA in patients with PBC with moderate to severe hepatic impairment. The current recommended dosing of such patients is

based on modeled systemic and hepatic concentrations. Therefore, Study 747-401 is specifically designed to characterize the PK, safety, and efficacy of OCA in this patient population.

PK and safety parameters will be evaluated as the primary objectives and efficacy parameters will be evaluated as secondary and additional objectives. While the prognostic utility of ALP has been established by the Global PBC study group, increasing levels of bilirubin are more relevant to understanding the progression of end stage liver disease. Consistently, bilirubin is a key marker of advancing disease as characterized by the Global PBC study group as well as its incorporation into model of end stage liver disease (MELD), Child-Pugh (CP), and Mayo risk scores. As such, the potential of OCA to stabilize bilirubin levels will be evaluated.

In order to generate data for the patient population in a timely fashion, Study 747-401 is designed with a relatively short-term, 1-year double-blind treatment period to gather primarily PK and safety data. Therefore, the study will not formally test the long-term efficacy of OCA on clinical outcomes.

Although Study 747-401 is not designed to formally evaluate clinical outcomes, these data will be collected and assessed as an additional objective. Given the importance of evaluating clinical outcomes in patients with the most advanced form of the disease, these events will be prospectively adjudicated consistent with the procedures implemented in ongoing PBC studies. This will allow for a more robust meta-evaluation of clinical outcomes in patients with moderate to severe hepatic impairment following the completion of both studies.

Study 747-302 is specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment. Data collected from Study 747-401 will serve as a bridge to the 747-302 study.

Taken together, data from this study will complement the data from Study 747-302 and offer the opportunity to better inform the benefit risk profile and appropriate treatment of hepatically-impaired patients.

5.4.2. Rationale for Obeticholic Acid Dose and Duration

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (CP Score). Model simulations predicted that for mild (Child-Pugh A [CP-A]), moderate (Child-Pugh B [CP-B]), and severe (Child-Pugh C [CP-C]) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to patients with normal hepatic function, whereas total OCA liver concentrations increase 1.1-, 1.5-, and 1.7-fold, respectively. Because the liver is the primary site of action for the safety and efficacy of OCA, it is important to account for the differences in systemic and liver exposure when assessing effective doses. It is also important to note that while hepatically impaired (CP-B and C) patients treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy patients, no apparent impact on the overall safety profile was observed, consistent with only a modest increase in liver exposure of OCA associated with hepatic impairment. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).

The dosing regimen in this study follows the FDA-approved prescribing information, with the exception of the maximum allowed dose in patients with moderate impairment. While the prescribing information allows for a maximum dose of 10 mg twice weekly for patients with moderate impairment, the protocol allows for a maximum dose of 5 mg once daily. The choice of 5 mg once daily is supported by the estimated steady-state liver and plasma exposure of total OCA for patients with moderate hepatic impairment receiving a 5 mg once daily dose relative to healthy patients receiving a 10 mg dose. A maximum allowed dose of 5 mg once daily in patients with moderate hepatic impairment is estimated to achieve liver exposure similar to non-hepatically impaired patients receiving a 10 mg daily dose and maximize efficacy in this patient population.

5.4.3. Rationale for Population Chosen

Patients with PBC and moderate or severe hepatic impairment, based on CP score and varying levels of MELD, are the targeted population for this study as OCA has been studied primarily in early to moderate stages of liver impairment in patients with PBC. There is a great need to extend therapies to PBC patients with more advanced liver impairment. Given the unmet medical need and observed efficacy, safety and tolerability profile of OCA in early and moderate PBC, evaluating the effects of OCA in a late stage population is warranted.

5.4.4. Rationale for Control Group

The use of a randomized placebo control group added to established standard of care provides the best scientific evidence of efficacy and safety. The use of a placebo control provides a concurrent comparator group, accounting for not only a placebo effect but continued standard of care. The use of a placebo control is critical to assess the safety and tolerability of OCA but also as a comparator for the high rate of clinical events which are expected in this advanced population.

5.5. Summary of Known Potential Risks with Investigational Product

The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy patients, but with a much lower frequency than that observed in patients with PBC.

Consistent with the dose-limiting hepatic toxicities observed in the non-clinical studies and the chemical characteristics of OCA as a bile acid and detergent, dose-related but reversible and asymptomatic increases in ALT and AST were observed in healthy volunteers treated with multiple doses of OCA starting at the 100 mg dose (Study 747-102).

In patients with chronic liver disease such as PBC, hepatobiliary findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed. These findings were seen more frequently with doses

of OCA 10 mg once daily to OCA 50 mg once daily (up to 5x the highest recommended dose). In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.

Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDLc) and an increase in low density lipoprotein (LDLc). Notably, in patients with PBC, the decrease in mean HDLc levels occurred early and stabilized within 3 months after which time levels generally remained constant over the course of treatment. The average levels of HDLc remained within normal limits. Commensurate with decreases in HDLc, decreases in total cholesterol were observed in patients with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA treated patients with the exception of a modest transient and early rise after initiation of treatment.

Based on previous PK and short-term studies in patients with hepatic impairment, increased systemic exposure was not associated with an apparent change in the safety profile of OCA as assessed by the incidence and severity of AEs or by changes in clinical laboratory tests. Hepatotoxicity has been associated with increased liver concentrations of OCA. Hepatic impairment does not affect the ability of OCA to activate FXR in the intestine and the liver.

Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

The study will be conducted in patients with PBC and moderate to severe hepatic impairment defined as CP-B and CP-C with MELD scores ranging from 6 to 24.

6.1. Primary Objectives

- To evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and OCA metabolite glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

6.2. Secondary Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - The MELD score and its components
  - CP score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

6.3. Additional Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - Markers of inflammation
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD Parameters and Safety and Tolerability assessments
- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ]
- To assess clinical events consistent with end-stage liver disease
  - Death (all-cause)
  - Liver transplant
  - Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≥12 at baseline)
  - 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
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with PBC and moderate to severe hepatic impairment defined as CP-B and CP-C including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

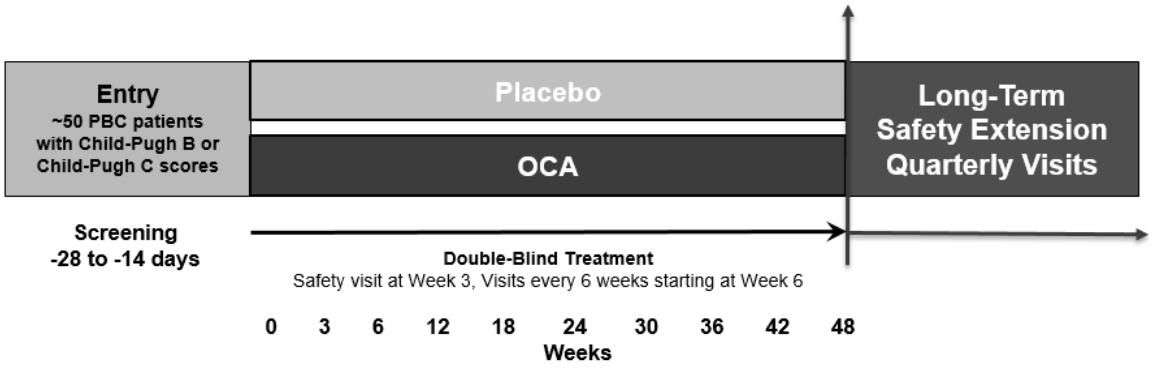
Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Treatment Period: During the 48-week treatment period, an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. At each visit (except screening and Week 3), fasting PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12, 18, 24, 30, and 48.

Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. Patients will then be given the option to go on open-label treatment.

7.1.1. Study Design Diagram

Figure 1: Study Design



OCA = obeticholic acid, PBC = primary biliary cholangitis
Note: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score.
Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

			Treatment Period (Weeks)								Long-Term Safety Extension
	Screening	Day 1[a,b]	3[c]	6[d]	12	18	24	30	36	48/ ET/ EOS/EOT	Every 3 months
Visit Window (+/-)	**-28 to -14 days**		**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±2 wks**
Fast ≥8 h Prior to Visit[e]	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X										
Medical/PBC History	X										
Inclusion/Exclusion Criteria	X	X									
Physical Exam[f]	X	X		X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X		X	X	X	X	X	X	X	X
Medical and Surgical Procedures		X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Assessments for Child-Pugh Score[g]	X	X		X	X	X	X	X	X	X	X
Patient Questionnaires (Pruritus VAS, PBC-40, EQ- 5D-5L, and CLDQ)[h]		X		X	X	X	X	X	X	X	X
Randomization/Treatment Assigned		X									
Dispense IP[i]		X			X	X	X	X	X	X	X
Dose Titration Assessment[j]					X	X	X	X	X	X	X
IP Accountability/ Compliance			X	X	X	X	X	X	X	X	X

Table 1: Schedule of Study Procedures (Continued)

			Treatment Period (Weeks)								Long-Term Treatment
	Screening	Day 1[a,b]	3[c]	6[d]	12	18	24	30	36	48/ ET/ EOS/EOT	Every 3 months
Visit Window (+/-)	**-28 to -14 days**		**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±2 wks**
Urinalysis (dipstick)	X	X								X	X[o]
Urine-based β-hCG Pregnancy Test[k]	X	X		X	X	X	X	X	X	X	X
Virology (HCV/HBsAG)	X										
Serum Chemistry/Hematology/ Coagulation	X	X	X	X	X	X	X	X	X	X	X
Markers of Inflammation: IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30		X			X		X		X	X	
PK Fasting Collection		X		X	X	X	X	X	X	X	
PK Serial Collection[l]					X	X	X	X		X	
PD Markers: Bile Acid/C4/FGF-19		X		X	X	X	X	X	X	X	
TE/ELF (HA, P3NP, and TIMP-1)[m]		X			X		X		X	X	X[n]
12-Lead Electrocardiogram	X									X	X[o]
Hepatic Ultrasound[p]	X						X			X	X[n]

AE = adverse event; eCRF = electronic case report form; C4 = 7α hydroxy-4-cholesten-3-one; CK 18 M30 = cytokeratin-18 neoepitope M30; CLDQ = Chronic Liver Disease Questionnaire; ELF = enhanced liver fibrosis; ET = Early Termination; EOS = End of study; EOT = End of Treatment; ; FGF-19 = fibroblast growth factor-19; HA = hyaluronic acid; HCV = Hepatitis C virus; hs-CRP = high-sensitivity C-reactive protein; IL-6 = Interleukin 6; IP = Investigational Product; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; P3NP = procollagen 3 N-terminal peptide; PBC = primary biliary cirrhosis; PK = pharmacokinetics; TE = transient elastography; wk(s) = week(s), TNF-α = tumor necrosis factor-α; TIMP-1 = tissue inhibitor of metalloproteinase ; VAS = Visual Analogue Scale.

[a] Visit schedule should be based on Day 1. Day 1 visit must occur at least 2 weeks after screening visit.

[b] Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 9 and continuing to Week 48 to assess for AEs, concomitant medications, medical/surgical procedures, and verify that s/he is dosing as directed. (see Section 9.7.8).

[c] Preferably, the patient comes in to the clinic for this visit. Alternatively, site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.

[d] Visit should occur 3, 4, or 5 days after taking the Week 6 dose.

[e] The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, including screening, but water is permitted.

[f] Height and assessment of smoking and alcohol consumption history and current habits will be assessed at Screening and Week 48. Assessment of smoking and alcohol consumption history and current habits will be assessed quarterly after Week 48.

[g] Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF.

[h] The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease.

[i] New investigational product bottles will be dispensed if the patient is up-titrated. Unless up-titrated, patients are expected to use up each investigational product bottle before a new bottle will be dispensed. No new bottles will be dispensed if dose frequency is changed. Patients will be instructed to begin dosing on Day 1, after completing all study assessments. Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

[j] Dose titration of investigational product may occur starting after the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability, and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score.

[k] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit (except Week 3). If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally).

[l] The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling.

[m] The noninvasive radiological liver fibrosis measurement devices (such as, FibroScan® device [Echosens; Paris, France]) will be used at all study sites to collect hepatic stiffness measurements.

[n] Patients will complete a TE/ELF and ultrasound assessment, every 6 months (±2 weeks) after Week 48.

[o] ECG and urine dipstick will be done yearly (±2 weeks) after Week 48 Visit.

[p] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm suspected HCC.

7.1.3. Study Duration

Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment.

7.2. Number of Patients

Approximately 50 patients will be enrolled in this study.

7.3. Planned Dosing Regimen

All patients will initiate investigational product once weekly with OCA 5 mg or matching placebo (Table 2). Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on safety and tolerability assessments, patients can be considered for further up titration as described below (Table 2). At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.

Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.

Patients with CP-C may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply (Table 3).

Table 2: Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score

	Child-Pugh B (Moderate Hepatic Impairment)		**Child-Pugh C (Severe Hepatic Impairment)**	
	Treatment Group		**Treatment Group**	
	OCA	Placebo	OCA	Placebo
Starting Dose (Day 1)	5 mg once weekly	matching placebo	5 mg once weekly	matching placebo
Titration 1[a]	5 mg twice weekly[b]	matching placebo	5 mg twice weekly[b]	matching placebo
Titration 2[a]	10 mg twice weekly[b]	matching placebo	10 mg twice weekly[b]	matching placebo
Titration 3[a]	5 mg once daily	matching placebo	NA	NA

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

7.4. Dose Adjustment Criteria

Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns or as a result of changes in a patient's CP Score.

Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as assessed by a review of AEs and safety laboratory results). In general, down-titration may be done in response to tolerability concerns and can occur at any time. Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated for each dosing regimen as defined in Section 7.3.

Scheduled Dose Titration - After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose or dosing frequency for patients may occur no earlier than 6 weeks following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability)

Dose Titration due to Change in CP Score – Over the course of the study, a patient's CP category may change. When a patient demonstrates a change in CP category (as assessed per Table 10), dosing should be reassessed and modified if appropriate (Table 2). Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply (Table 3). If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen (Table 2) should be followed.

Table 3: Maximum Daily dose based on change in Child-Pugh Category

Original Status	New Status[a]		
	Child-Pugh A	Child-Pugh B	Child-Pugh C
Child-Pugh B	*No change*	*No change*	10 mg twice weekly
Child-Pugh C	5 mg once daily	5 mg once daily	*No change*

[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.3 .
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

CP Scores will be calculated at all study visits (except Week 3). While PBC-specific versions of CP scores are available, this study will use the standard calculation (Pugh 1973, Lucey 1997). All associated visit data (including central laboratory results) should be entered into the electronic case report form (eCRF) in a timely fashion to confirm that the patient's CP Score has

not changed. If a change in CP Score is observed independent of a study visit, the patient should be contacted via phone to discuss the need for a dosing modification and should be asked to return to the investigative site as soon as possible if a new bottle of investigational product is required to be dispensed.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. To determine if a patient is eligible for a dose up-titration refer to Section 7.3.

7.5. Criteria for Study Termination

The Sponsor (Intercept Pharmaceuticals, Inc.) reserves the right to terminate the study at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the Data Monitoring Committee (DMC), it may be necessary to stop the study before all patients have completed the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, Good Clinical Practice [GCP] noncompliance or poorly performing sites, as determined by the number of patients enrolled or the quality of the study data).

The Investigator and/or Sponsor (or designee) must notify the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of discontinuation of a site or the study and the reason for doing so.

Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all patients for the end of study (EOS) or end of treatment (EOT) Visit.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Population

This study will be conducted at approximately 35 international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B and CP-C. Prospective patients will be identified primarily from the hospital and/or physician's database of patients with PBC, or may be referred from other physicians. Patients may self-refer to an Investigator if they become aware of the study through local, national, or international PBC patient societies, forums, or networks.

8.2. Patient Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines [Lindor 2009, EASL 2009]), defined as having ≥2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or

antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)

- Liver biopsy consistent with PBC (collected at any time prior to Screening)

2. Evidence of cirrhosis including at least one of the following:
   - Biopsy results consistent with PBC Stage 4
   - Liver stiffness as assessed by TE Median Value ≥16.9kPa
   - Clinical evidence in the absence of acute liver failure consistent with cirrhosis including: gastroesophageal varices, ascites, radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
   - Combined low platelet count (<140 000/mm^3) with
     - persistent decrease in serum albumin, or
     - elevation in prothrombin time /INR (not due to antithrombotic agent use), or
     - elevated bilirubin (2× ULN)
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening (ie, within 14 days before the first dose of investigational product):
   - Moderate: CP-B (Scores 7 to 9) or
   - Severe: CP-C (Scores 10 to 12)
4. MELD score of 6 to 24 at Screening
5. Age ≥18 years
6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate or unresponsive to UDCA (no UDCA for ≥3 months)
7. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) with spermicide **or** (b) diaphragm with spermicide; or
   - Intrauterine device; or
   - Vasectomy (partner); or
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
   - Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)
8. Must provide written informed consent and agree to comply with the study protocol.

8.3. Patient Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. Hepatic encephalopathy (as defined by a West Haven score of ≥2 [AASLD, EASL 2014])
5. History or presence of other concomitant liver diseases including:
    a. Hepatitis C virus infection and RNA positive
    b. Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the medical monitor
    c. Primary sclerosing cholangitis
    d. Alcoholic liver disease
    e. Definite autoimmune liver disease or overlap hepatitis
    f. Gilbert's Syndrome
6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function prior to randomization
7. Patients with history or presence of hepatorenal or hepatopulmonary syndrome
8. Patients with significant active infection (ie spontaneous bacterial peritonitis)
9. Patients with known or suspected hepatocellular carcinoma
10. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
11. Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study
12. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
13. UDCA naïve (unless contraindicated)

8.4. Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study

Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.

Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling, but may withdraw consent at any time.

8.4.1. Reasons for Additional Monitoring or Mandatory Interruption of Investigational Product

8.4.1.1. Reasons for Additional Monitoring Related to Liver Chemistries

Patients who develop ALT or AST >2× baseline (and >ULN) or total bilirubin >1.5× baseline (and >ULN) should have repeat testing within 48 to 72 hours to confirm values. Patients with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or INR with persistent increases in ALT or AST should also be closely monitored.

8.4.1.2. Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries

Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:

- AST and/or ALT >3× baseline (and >ULN)
- Total bilirubin >2× baseline (and >ULN)

Repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing should be performed. Detailed adverse event information should also be collected, and the patient should be investigated for possible causes of the liver chemistry changes, as appropriate. The Investigator should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable.

If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), patients should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms.

For the purposes of this protocol, if the above referenced significant elevation in liver enzyme or bilirubin levels resolve following interruption of investigational product and no other cause for the elevation is identified, the elevations should be assumed to be related to investigational product and investigational product should be discontinued. If the liver enzyme or bilirubin levels do not resolve following interruption of investigational product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the patient may be re-challenged following a discussion between the Investigator or designee and the Sponsor.

Elevation of liver enzymes or bilirubin is based on comparison to baseline values defined as the mean of all available Screening and Day 1 values, which are the mean of all available evaluations prior to the first administration of investigational product. At least 2 of these samples will be obtained a minimum of 2 weeks apart during the Screening period. Elevations that occur gradually over the course of the study may be indicative of disease progression and should be assessed as clinically appropriate. Liver enzyme and bilirubin elevations that occur over a shorter time, such as within a 6-month period, should be evaluated for drug-induced liver injury as provided in the guidelines below.

If at any time a patient develops signs or symptoms of hepatotoxicity such as new onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>7%) in combination with elevations in liver enzymes, investigational product should be interrupted and liver enzymes monitored until signs or symptoms resolve.

Patients who develop evidence of severe drug-induced liver injury that is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged. Severe drug-induced liver injury includes, but is not limited to, functional hepatic impairment, as indicated by rising bilirubin or INR that cannot be explained by progression of disease. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.

If after all investigations and actions outlined above have been completed, the investigator determines that the elevations in liver biochemistries are considered not related to investigational product, the Sponsor must be contacted before investigational product can be reinitiated. Follow-up procedures for patients resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment. Results must be reported to the site as soon as possible so the Investigator can determine if it is appropriate for the patient to continue treatment.

The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.

All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 15.9).

8.4.1.3. Pregnancy

If a female patient becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 13.1.9 pregnancy is not considered an AE for reporting purposes. The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 13.1.9). New baseline procedures should include pregnancy testing.

8.4.2. Reasons for Mandatory Discontinuation of Investigational Product

Patients who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these patients should be encouraged to consent to the semiannual telephone contact and/or continued record review only to allow for secondary outcome events data to be collected.

8.4.3. Other Reasons for Discontinuation of Study or Investigational Product

The following events are considered appropriate reasons for a patient to discontinue investigational product; however, these patients are expected to continue in the study until study termination (or at the discretion of the Sponsor):

- Patient begins treatment with commercially available OCA.

- The Investigator or Sponsor considers that it is advisable or in the best interest of the patient.
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to study drug.
- Withdrawal of consent
  - Consent may be fully withdrawn (in which case the patient discontinues both investigational product and study visits and procedures).
  - Consent may be modified to discontinue study visits but allow semi-annual telephone contact.
  - Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE) and liver-related clinical events.
  - Early termination procedures should be conducted if the patient withdraws consent (see Section 9.7.13).

The Investigator is encouraged to contact the Sponsor prior to discontinuing a patient from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any patient prematurely withdraws from the study.

8.4.3.1. Withdrawal of Consent to Continue in the Study

If the patient decides that it is in his/her best interest to discontinue from the study, he or she may withdraw consent. It is fully understood that all patients volunteer for the study and that they may withdraw their consent to continue in the study at any time.

Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.13).

A reasonable effort must be made to determine the reason(s) for patient discontinuation. This information and date must be recorded in the appropriate eCRF.

8.4.3.2. Lost to Follow-Up

Patients will be considered “lost to follow-up” only after documented attempts to reach the patient prove unsuccessful. A reasonable effort (ie, 2 phone calls/messages, no response to registered letter) must be made to contact the patient and determine the reason(s) why a patient fails to return for a study visit or is lost to follow-up. This information and date of contact must be recorded in the appropriate eCRF.

8.4.4. Patient Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. This information must be documented in the eCRF.

If a patient is withdrawn from the study early (regardless of the cause), all of the early termination (ET)/EOS evaluations are to be performed at the time of withdrawal, to the extent possible.

9. TREATMENT OF PATIENTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or placebo.

Two treatment groups will be evaluated: OCA and placebo. Investigational product will be administered orally. Each dose will be made up of 1 tablet (ie, one OCA 5 mg tablet or one OCA 10 mg tablet, or matching placebo).

Investigational product will be taken orally with water for the duration of the study. Patients will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time on dosing days. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.2) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications (including prescribed, over the-counter, or herbal preparations) taken within 30 days of Screening and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 1.

PBC Specific Therapy

Investigators will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. Throughout the course of the study, Investigators are expected to monitor patients' PBC regimens and, if responsible for usual care, may adjust the regimen to achieve locally-appropriate treatment goals. These goals will be individualized, with the understanding that currently applicable PBC guidelines may vary across different geographic regions.

Ideally, patients should generally remain on the baseline PBC therapies throughout the course of the study, unless the baseline PBC therapy is no longer considered clinically appropriate by the Investigator. In addition, patients should be reminded to keep taking their blinded investigational product.

9.2.1. Drug Interactions

Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should not be taken within 4 hours of taking investigational product (and UDCA if applicable), ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration.

OCA taken concomitantly with warfarin may result in decreased INR levels; therefore, INR should be monitored and the dosage of warfarin adjusted, as needed during treatment with OCA and after cessation of OCA, to maintain the target INR range.

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate probe, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

Information related to additional drug-drug interaction (DDI) studies is available in the current version of the IB. The aforementioned sections of the IB should be referred to during the course of the study, and are accessible to Investigators to help facilitate the assessment of potential DDIs with OCA that may be observed in study patients.

9.2.2. Prohibited Medications

Commercial OCA therapy (if available) is prohibited while on investigational product, and if prescribed during the course of the study, the Investigator should be cognizant of the possibility of double dosing. Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.3).

9.3. Treatment Compliance

The Investigator should assess the patient's compliance with dosing of investigational product at each study visit, and confirm by conducting investigational product accountability (ie, count of returned tablets).

Patients should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the indicated visits (Table 1). The Investigator or designee should perform investigational product accountability (ie, count of returned tablets) and, if applicable, follow-up with the patient to retrieve any investigational product bottles that have not been returned.

If the Investigator has concerns about a patient's dosing compliance, he or she should discuss this with the patient, assess the reasons for noncompliance and the likelihood that the patient will remain noncompliant, and notify the Sponsor accordingly.

9.4. Randomization and Blinding

9.4.1. Methods of Assigning Patients to Treatment Groups

This study will be conducted in a double-blind, placebo-controlled manner. Enrolled patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: placebo or OCA based on a predefined randomization code (generated by Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based patient registration system at Screening and Day 1.

Randomization will be stratified by CP class (CP-B or CP-C). Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores. The IWRS will serve as the investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the patient in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the patient to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind.

9.4.2. Blinding

The Sponsor, patients, Investigator, and study site staff will be blinded to the patient's treatment allocation during the patient's participation in the double-blind phase of the study.

9.4.3. Emergency Unblinding Procedures

Treatment assignment for individual patients will be made available to the Investigator for medical emergency use only (such as unblinding which is necessary in order to treat an serious adverse event [SAE] through the IWRS system). When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment assignment is necessary for further medical management of the patient). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the patient's record the rationale for unblinding and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment. Procedures for unblinding a patient's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual patient for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The DMC will have access to the IWRS and will be able to unblind individual patients. Refer to Section 15.8 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded patient data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the study is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DMC.

Access to treatment assignments will also be made available to the designated Intercept staff responsible for expedited safety reporting of suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

9.5. Assignment of Site and Patient Numbers

9.5.1. Site Numbers

Each study site selected to participate in this study will be assigned a site number by the Sponsor. The site number will be used to categorize patient data and to identify the site and/or Investigator within study documents. This number will be recorded in the eCRF.

9.5.2. Patient Numbers

Patients will be identified by a unique 6-digit number, independent of the randomization number. The first 3 digits will represent the site number and the last three digits will represent the Screening number.

9.6. Restrictions

Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited. Previous exposure to OCA (as a study participant or received commercial OCA therapy) is allowed provided patients haven't taken OCA within 3 months prior to enrollment in this study.

9.6.1. Fasting Requirement at Study Visits

All patients must have been fasting for at least 8 hours prior to their Screening Visit and all subsequent study visits, as all analytes will be assayed in fasting blood or plasma samples. Water is permitted during the fasting period.

9.7. Visit Procedures

9.7.1. Visit Windows

Visit windows are specified in the Schedule of Study Procedures (Table 1). Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. For example, Week 6 should ideally occur 6 calendar weeks (± 7 days) following Day 1.

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed

consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated consent form. Patients will also be provided a separate ICF before providing blood samples for genetic analysis and must be willing and able to provide consent as described above.

9.7.3. Assessing Cirrhosis

Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators:

- Biopsy results consistent with PBC Stage 4 (Ludwig 1978)
- Transient Elastography Median Value ≥16.9 kPa (Corpechot 2012)
- The presence of any of the following (unless exclusionary per Section 8.3) in the absence of acute liver failure:
  - Gastroesophageal varices
  - Ascites
  - Radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
- Combined low platelet count (<140 000/mm^3) with:
  - persistent decrease in serum albumin, or
  - elevation in prothrombin time /INR (not due to antithrombotic agent use), or
  - elevated bilirubin (2× ULN)

9.7.4. Screening Procedures (14 days to 28 days prior to Day 1)

Informed consent must be obtained from the patient before performing any study-related procedures, including Screening procedures. The Screening Visit assessments must be performed ≥14 days but less than 28 days prior to Day 1 to determine whether the patient meets all the inclusion criteria and none of the exclusion criteria. Patients who do not fulfill all eligibility criteria will not be enrolled in the study. Patients may be rescreened after 2 months have elapsed from the date of their most recent screening visit procedure; however, all Screening procedures (including obtaining informed consent) should be repeated and a new three-digit Screening number assigned.

Screening Visit procedures are as follows:

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Collect medical history.

- Collect PBC history.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination, including height, smoking and alcohol consumption history, and current habits for both.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Perform a standard 12-lead electrocardiogram (ECG).
- Perform assessments for calculation of CP Score (Section 14.1.1)
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Virology Screen (HCV and HBsAg)
- Obtain urine sample for urinalysis (dipstick).
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test in females of childbearing potential.
- Instruct the patient to fast overnight (at least 8 hours) before the next visit (water is permitted).
- Record the visit in IWRS.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required. If the ultrasound cannot be performed at Screening (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed anytime within the screening visit window or on Day 0. Results from the screening ultrasound should be reviewed to assess possible exclusion criteria prior to randomization.

9.7.5. Day 1 Procedures (Randomization)

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Review inclusion and exclusion criteria for eligibility.
- Perform a physical examination.

- Review and record any non-study related medical or surgical treatment procedures and any medically relevant heath care professional (HCP) or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (Section 13.2.6).
- Randomize the patient only if s/he meets all inclusion criteria and no exclusion criteria.
- Record the visit in IWRS and dispense investigational product
  - Instruct the patient to begin dosing on the day of the Day 1 Visit.
- Obtain urine sample for urinalysis (dipstick).
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of inflammation and fibrosis (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30, ELF [HA, P3NP, and TIMP 1])
  - Fasting PK assessment
  - Bile Acid/C4/FGF-19
- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.6. Week 3 Safety Visit Procedures

Preferably, the patient will come in to the clinic for this visit. Alternatively, the site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.

- Verify that patient is dosing as directed.
- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Review and record prior concomitant medications.
- Assess and record AEs.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
- Schedule the next visit (Week 6), reiterate dosing instructions, and advise the patient:

  Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 2).
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.7. Week 6 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).

- Assess and record AEs.
- Review and record concomitant medications.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.6).
- Assess investigational product compliance, perform investigational product accountability.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Bile Acids/C4/FGF-19
  - Fasting PK assessment
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.8. Week 9 through Week 48 (Safety Contact)

Patients should be contacted by telephone/email at Week 9 and every 3 weeks afterward to Week 48.

- Contact patient by phone/email.
- Review and record prior concomitant medications.
- Assess and record AEs.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.

9.7.9. Week 12, Week 24, Week 36 Procedures

- Verify that the patient has fasted for at least 8 hours.

  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.6).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible. (Refer to Section 7.3)
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of inflammation and fibrosis (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30, ELF [HA, P3NP, and TIMP 1])
  - Bile Acid/C4/FGF-19
  - Fasting PK assessment
- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit.
- Perform an ultrasound for HCC surveillance at **Week 24 ONLY** (if equipment is unavailable, sites should make every attempt to use available community referral sites).

- Serial PK assessment **at Week 12 and 24 ONLY (not done at Week 36 and Week 42)**; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose

Note: Patients should only consume a meal following the 4-hour and 7-hour PK assessment times (see Figure 3). Patients should not drink any water until at least one hour postdose.

- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.10. Week 18 and Week 30 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.6).

- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Bile Acid/C4/FGF-19
  - Fasting PK assessment
- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose

Note: Patients should only consume meal following the 4-hour and 7-hour PK assessment times (see Figure 3). Patients should not drink any water until at least one hour post dose

- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.11. Week 48 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF

  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.

- Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform ECG.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.6).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform urinalysis (dipstick)
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of inflammation and fibrosis (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30, ELF [HA, P3NP, and TIMP 1])
  - Fasting PK assessment
  - Bile Acids/C4/FGF-19
- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose

- Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes)
- Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose

Note: Patients should only consume meal following the 4-hour and 7-hour PK assessment times (see Figure 3). Patients should not drink any water until at least one hour post dose

- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data are needed for cirrhosis assessment) or as close as possible to the visit.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.12. Every 3 Months after Week 48

Quarterly

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).

- Administer Quality of Life and Patient questionnaires (see Section 13.2.6).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

Patients will complete a TE/ELF (HA, P3NP and TIMP 1) and ultrasound (for HCC surveillance) assessment, every 6 months (±2 weeks) after Week 48.

ECG and urine will be done yearly (±2 weeks) after Week 48.

9.7.13. End of Study/Early Termination/End of Treatment Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent

Patients who discontinue investigational product before Week 48 are expected to continue in the study until the end of the study (EOS [when subject terminates the study]) or at the discretion of the Sponsor.

EOT (when subject discontinues investigational product)/ET procedures will be required whenever patients discontinue treatment with investigational product (Table 1, Section 9.7.11). The EOT/ET Visit (Table 1) and procedures listed below (Table 4) must be performed as close as possible to the patient's last dose of investigational product. When a patient discontinues or interrupts investigational product and continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. The actual investigational product discontinuation scenario (Table 4) will determine the sequence of the EOT/ET and EOS Visits and procedures. In some cases, the EOT/ET Visit and procedures will precede the EOS Visit; in others, the EOT/ET and EOS Visits will be combined and performed as close as possible to the patient's last dose of investigational product. EOT and EOS Visits are encouraged but at no time will a missed EOT or EOS visit be considered a protocol deviation.

When a patient ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (ET) (withdrawal of consent) or discontinuation, an

EOT/EOS Visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. The purpose of this visit is to conduct complete and/or final assessments on or as near as possible to the final day of dosing. In some cases, the patient may discontinue on the day of a scheduled study visit. In these cases, EOT/EOS Visit procedures should be performed in place of the scheduled study visit procedures. The data will be recorded as EOT/ET and EOS procedures in the eCRF.

Table 4: Early Discontinuation Scenarios

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Early Termination	Discontinued	Withdrawn	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product.	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose of investigational product.	Complete at final study visit.
	Discontinued	Record review only	Record review only	Combined visit, completed as close as possible to last dose of investigational product.	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product.	
Pregnancy	Discontinued	Complete per the above scenarios - Early Termination or Treatment Discontinuation			
Lost to Follow-Up	Discontinued	LTF	None	Unable to complete due to LTF status	

EOS = end of study; EOT = end of treatment; LTF = lost to follow-up
[a] Refer to Section 7.1.2, Schedule of Study Procedures for all procedures and evaluations required at the EOS and EOT Visits.
[b] Includes initiation of commercially available OCA.

9.7.14. Unscheduled Safety Visit

The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted.

As appropriate, the Medical Monitor should be contacted.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

The investigational product is a white, round, film coated tablet containing OCA 5 mg or 10 mg or matching placebo. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

10.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to Good Manufacturing Practice standards by a designated qualified vendor. All investigational product will be provided as tablets for oral administration and provided in high density polyethylene bottles with heat induction seals and child resistant closures. The bottle packaging will not reveal any information about the treatment dose contained in the bottle. Multiple bottles may be dispensed to the patient at each visit to provide enough tablets for dosing until the next visit.

The designated investigational product packaging/distribution vendor will also be responsible for the distribution of the investigational product to the Investigator.

10.3. Investigational Product Storage

All OCA tablet strengths provided to clinical study sites in support of clinical studies are to be shipped and stored at 15˚C to 25˚C. Temperature excursions within the range of 2˚C and 30˚C for no more than a 6-month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20˚C to 40˚C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.

10.4. Investigational Product Administration

Refer to Section 9.1.

10.5. Investigational Product Accountability and Disposal

The Sponsor's representative will send investigational product to the study site under appropriate storage conditions. All shipments of investigational product should be unpacked and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product against the shipment documentation. The pharmacist or designee should contact the Sponsor immediately to report any concerns regarding the shipment.

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of investigational product accountability, including records of individual patient dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the Clinical Research Associate (CRA), will review accountability records against investigational product dispensed and that remaining in stock, during on site monitoring visits and when the study is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the investigational product. If the investigational product is to be returned to the Sponsor's vendor for destruction, the CRA will also prepare the investigational product for shipment.

11. OVERVIEW OF ASSESSMENTS

The assessments supporting the objectives for the study are in Table 5:

Table 5: Table of Assessments

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates glyco-OCA and tauro-OCA, and metabolite OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus, and fatigue
Secondary Objectives	**Assessments**
Changes in risk scores	Changes in MELD and CP Score components
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma bile acids
Additional Objectives	**Assessments**
Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30,
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	Transient Elastography/ELF (HA, P3NP, and TIMP-1)
PK/PD relationship	PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)
Patient-reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
Clinical events	Death (all-cause and liver-related), liver transplant, Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline), Hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, Uncontrolled ascites, and HCC.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope-M30; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; hs-CRP = high-sensitivity C-reactive protein; IgA = immunoglobulin; A IgG = immunoglobulin G; IgM = immunoglobulin M; IL-6 = interleukin 6; INR = international normalized ratio; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PBC = Primary Biliary Cholangitis; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TE = Transient Elastography; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; TNF-α = tumor necrosis factor; VAS = visual analog scale

12. CLINICAL PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic analyses will be based on the PK population (Section 15.1). Patients in the PK Population with at least one PD assessment after dosing will be included in the combined PK/PD analyses.

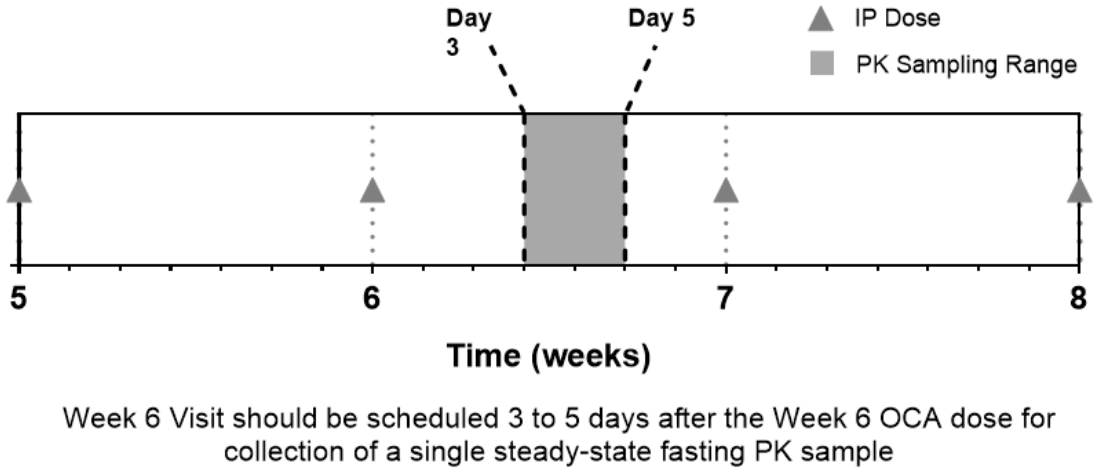
12.1. Pharmacokinetic Blood Sampling

Serial and fasting PK assessments will be performed in all patients participating in the study.

At Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48, patients will provide fasted blood samples for measurement of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide 30 minutes before administration of investigational product (predose for ≥12 weeks) (Table 6). Patients will then receive a dose of investigational product with approximately 240 mL of water.

Week 6 Visit should occur 3, 4, or 5 days **after** the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure 2]).

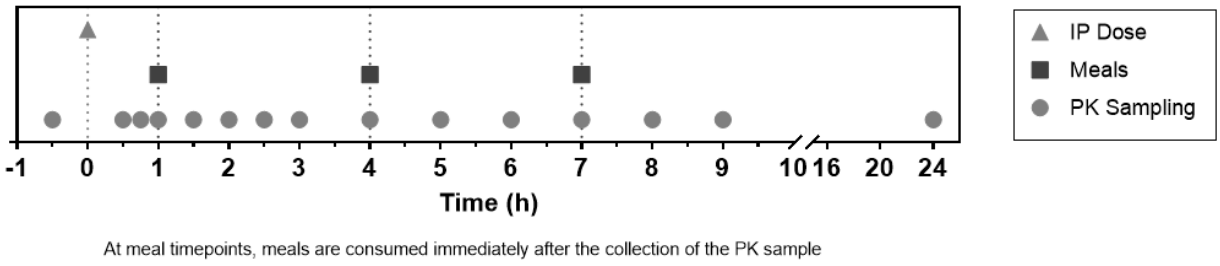
Figure 2: Week 6 Sampling Schedule



IP = investigational product; PK = pharmacokinetic

At Weeks 12, 18, 24, 30, and 48, serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose (Figure 3) for all patients. The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. The home health care agency must be advised one week in advance of the appointment.

Figure 3: Pharmacokinetic Sampling Schedule



h = hour; IP = investigational product; PK = pharmacokinetic

Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be

provided following collection of the 1-, 4-, and 7-hour PK sample; the meal will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 7-hour sample collection.

During the treatment period:

- Pharmacokinetic fasting samples will be obtained from all patients at Weeks 6, 12, 18, 24, 30, 36, and 48 prior to dose administration in accordance with Figure 3 .
- Serial PK assessments will be performed in all patients at Weeks 12, 18, 24, 30, and 48.

Table 6: Acceptable Windows for Pharmacokinetic Sample Collection

Nominal Sampling Time	Acceptable Sampling Window
Before administration of investigational product (predose or fasting)	Within 30 minutes before dosing
0.5 to 1.5 hours after investigational product	± 10 minutes
2 to 2.5 hours after investigational product	± 20 minutes
3 to 24 hours after investigational product	± 30 minutes

12.2. Processing and Handling of Pharmacokinetic Samples

Whole blood will be collected at each scheduled sample timepoint. Detailed procedures for the collection of blood samples including further processing into plasma will be provided in a separate laboratory manual. The storage and shipment procedures for subsequent bioanalysis, will be provided to the investigational site and home health care company in a separate document before the study is initiated.

12.3. Bioanalysis

Plasma concentrations of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide will be determined using a validated liquid-chromatography mass spectrometry/mass spectrometry (LC/MS/MS) method. A detailed description of validation information and results from the bioanalytical assay will be provided in separate reports. These samples may be used for evaluation of metabolites of OCA or other concomitant medication, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by OCA.

13. ASSESSMENT OF SAFETY

13.1. Adverse Events and Serious Adverse Events

13.1.1. Definitions of Adverse Events

13.1.1.1. Adverse Event

AEs are defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to investigational product. An AE, also referred to as an adverse experience, can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) patient deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE.

Patients should be questioned about AEs in a general way, without leading the patient or asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

13.1.1.2. Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

13.1.1.3. Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

13.1.2. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 7. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as suspected adverse reaction (SAR). "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "definite," "probable," or "possible" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 7: Relationship of Adverse Events to Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; that is confirmed by stopping or reducing the dosage of the investigational product; and that could not be reasonably explained by the known characteristics of the patient's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product; that does not follow a known or suspected response pattern to the suspected investigational product; and that could reasonably be explained by known characteristics of the patient's clinical state.
Not Related	Any event that does not meet the above criteria.

13.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 8, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 8: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Causing no limitation of usual activities; the patient may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the patient may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

13.1.4. Reporting of Adverse Events and Serious Adverse Events

13.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the patient fully completes her/his study participation of the study.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

13.1.4.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

All SAEs must be reported to the Sponsor (including suspected liver-related clinical outcome events that qualify as serious). SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by:

- E-mail to the SAE email address: PPD
- Fax using a paper SAE report form: PPD

If an SAE is reported by fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Patient number
- Event term
- At least 1 criterion classifying the event as serious
- Name and title of the reporting individual
- Causal relationship to the investigational product

The Investigator will assess whether the event is causally related to the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of Safety Reports/Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to PPD or emailed to PPD as soon as possible.

The Investigator is responsible for submitting information on Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local country requirements. Documentation of the submissions to IRBs/IEC s must be retained in the appropriate study file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate investigative site study files or with the IB.

13.1.5. Additional Investigator Responsibilities for SAEs

The safety data recorded in the EDC represent the official record of all AEs and SAEs reported in the study. The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the patient's AE EDC. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Sponsor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for patient care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the Medical Monitor.

13.1.6. Notification of Post-Treatment SAEs for Patients Who Continue in the Study

Post-treatment SAEs that occur in patients who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2 .

SAEs that occur in patients who discontinue investigational product, initiate treatment with commercially available Ocaliva, and remain in the study must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

13.1.7. Notification of Post-Study SAEs

All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2.

13.1.8. Follow-Up of AEs and SAEs

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented on the eCRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

All patients showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

13.1.9. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must interrupt treatment with investigational product immediately (see Section 8.4.1.3) and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The patient must have a negative pregnancy test before restarting investigational product. If a patient's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy confirmed by a serum β-hCG test before restarting investigational product.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when and AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 13.1.4 must also be followed.

13.2. Other Safety Parameters

13.2.1. Medical History/Demographics

A complete medical history will be obtained from the patient at screening. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

13.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the visits specified in the Schedule of Study Procedures (Table 1). A basic physical examination should be performed, including all body systems pertinent to the patient. Smoking and alcohol consumption history and current habits will be recorded. Any clinically significant abnormality should be reported on the AE eCRF page for findings that appear after consent, and on the medical history eCRF for any finding present prior to consent.

13.2.3. Vital Signs and Weight

Vital signs (oral temperature, sitting heart rate, respiratory rate and sitting blood pressure [BP]) and weight will be assessed at indicated visits (Table 1). When taking heart rate, respiratory rate and BP readings, patients should be seated quietly for a minimum of 3 minutes before the readings are taken.

13.2.4. Electrocardiogram

Standard ECGs will be collected. The Investigator or designee will review the ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after Day 1 will also be documented as AEs and entered on the AE page of the eCRF.

Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time. Full instructions will be provided for forwarding the ECGs for central reading.

13.2.5. Laboratory Assessments

Except for Screening, patients will be instructed to attend each study visit in a fasted state, preferably in the morning, and patients should remain fasted until their blood samples have been collected. At all visits (except screening), the Investigator or designee will verify that the patient has fasted for at least 8 hours and record fasting status in the source and eCRF. If the patient reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and eCRF and remind the patient that fasting is required before all study visits.

Blood samples for serum chemistry, coagulation, and hematology; and urine samples will be collected at visits as detailed in the Schedule of Study Procedures (see Table 1). The number and volume of samples to be collected at each visit will be detailed in the laboratory manual.

Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

All patients with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.

Laboratory samples will be stored for a maximum of up to 1 year after the end of the study (depending on stability) in the event that retesting is required, and destroyed after 1 year if not analyzed.

The list of laboratory analytes to be tested is shown in Table 9.

Table 9: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen, creatinine, direct bilirubin, total bilirubin, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, TFT (TSH, free T3 and free T4)
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)
Coagulation	PT, PTT, INR
Urinalysis (dipstick)	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive), pregnancy
Markers of Inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	ELF (HA, P3NP, and TIMP-1) TE
PK assessments	OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)
PD markers	C4, FGF-19 and plasma bile acids

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CK-18-M30 = cytokeratin-18 neoepitope M30; CP = Child-Pugh; CPK = creatine phosphokinase; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; HDL = high density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-6 = Interleukin 6; INR = international normalized ratio; LGL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; OCA = obeticholic acid; PBC = primary biliary cirrhosis; P3NP = procollagen 3 N-terminal peptide; PT = Prothrombin time; PTT = partial thromboplastin time; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TE = Transient Elastography; TG = triglyceride; TFT = thyroid function test; TIMP-1 = tissue inhibitor of metalloproteinase 1; TNF-α = tumor necrosis factor-α, VLDL = very-low density lipoprotein

Laboratory reference ranges for the study will be based on the laboratory vendor range.

Urine based β-hCG pregnancy tests will be performed in female patients of childbearing potential per protocol specified visits (see Table 1). If a urine pregnancy test is positive, a serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified and the patient will be followed as outlined in Section 13.1.9 until pregnancy outcome.

INR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, Na, and INR values, with modification by

United Network for Organ Sharing. Total OCA will be calculated based on OCA, tauro-OCA, glyco-OCA, and metabolite OCA glucuronide concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.

13.2.6. Patient-Reported Outcomes and Healthcare Resource Use

Data will be collected to determine the effects of OCA on health-related quality of life. Healthcare resource use as well as a general health status assessment (for the purposes of generating health utilities) will be used to support subsequent cost-effectiveness analyses that are relevant to major health care systems around the world. Assessments of patient-reported outcomes will take place during the visits indicated in Table 1.

The following patient-reported outcomes will be used to evaluate the effects of OCA compared to placebo on improvements in health-related quality of life:

- PBC-40: The PBC-40 is a validated disease-specific 40-question quality of life questionnaire, which consists of 6 domains: General Symptoms, Itch, Fatigue, Cognitive Function, Social, and Emotional (Jacoby 2005).
- EQ-5D-5L: The EQ-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VASs). The descriptive system is organized into 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the patient's self-rated health on a 20-cm vertical, line with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman 2011, Oemar 2013).
- Pruritus VAS: A VAS will also be used to assess pruritus in individual patients.
- CLDQ: The CLDQ is a disease-specific health related quality of life questionnaire for patients with chronic liver disease. The questionnaire includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry). Each question is answered on a scale from 1 (always) to 7 (never) with a higher score corresponding to a better quality of life. The CLDQ produces a summary score and domain scores that correlate with the severity of liver disease (Younossi 1999).

Patients will be asked to complete the questionnaires and initial and date each document. The questionnaires should be filed in the patient's study records. These may require transcription to the eCRF by study site staff.

Healthcare resource use will be collected from eCRFs including number, reason for and duration of hospitalizations and emergency room visits, number of outpatient physician visits (patient reported), and use of concomitant medications. The purpose is to evaluate the effects of OCA compared to placebo on patient-reported outcomes and healthcare resource.

14. EFFICACY ASSESSMENTS

14.1. Biochemical Measures of Disease Severity

14.1.1. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 10 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory. Investigators will be responsible for determining the appropriate dosing regimen based on the CP score (Table 1 and Table 10). Any change in CP Score will necessitate re-evaluation of the dosing regimen.

Table 10: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Mild	Moderate-Severe
Hepatic encephalopathy[a]		0	Grade 1 or 2	Grade 3 or 4

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
(Pugh 1973, Lucey 1997)

14.1.2. Model of End Stage Liver Disease Score

The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is useful in assessing patients with significant decompensation, and the MELD score is now used by the United Network for Organ Sharing in the US and Eurotransplants to manage the organ allocation for liver transplantation. The threshold for placement on an organ transplantation queue varies between regions across the globe.

An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total

bilirubin, serum creatinine, and INR, as appropriate, to predict survival and is calculated according to the following formula (Kamath 2007):

MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43

MELD score will be calculated and reported in whole numbers according to the frequency listed in Table 1.

14.1.3. Changes in Liver Biochemistry and Hepatobiliary Damage

ALP, ALT, AST, GGT, total and direct bilirubin, INR, creatinine, albumin, platelets will be measured according to the frequency listed in Table 1.

14.2. Additional Assessments

14.2.1. Markers of Inflammation, Apoptosis and Necrosis

Blood samples for analytes including IL-6, hs-CRP, IgA, IgG, IgM, TNF-α, cytokeratin-18 neoepitope M30. Assessments will be performed according to the schedules presented in Table 1.

14.2.2. Noninvasive Measurements of Liver Stiffness and Fibrosis

The ELF test assesses: HA, P3NP, and TIMP-1. Samples will be assessed in patients according to the schedules presented in Table 1.

The Fibroscan® TE device (Echosens, Paris, France) will be used at all study sites that have the equipment to collect hepatic stiffness measurements. These study sites must have the staff trained in the use and data interpretation of the device. This is a validated and non-invasive technique used to assess hepatic fibrosis which will be conducted according to the schedule presented in Table 1.

14.2.3. Markers of FXR activation

Blood samples will be collected in all patients to measure C4, FGF-19, and bile acids. The results of these analyses will be used to assess the PK/PD response of OCA. Blood samples will be assessed in patients according to the schedule presented in see Table 1.

14.2.4. Clinical Outcome Events

Clinical outcome events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.

15. STATISTICAL METHODS AND ANALYSES

Individual patient data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by patient. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on treatment study days are numbered relative to the day of the first dose of investigational product which is designated as Day 1.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the ICH recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, Baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For continuous variables, the number of patients, mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more decimal place than the raw data, and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations.

There will be no formal hypothesis testing in this study. However, summary statistics for each treatment group will be presented, as well as 95% CIs for the difference between the treatment groups.

15.1. Analysis Populations

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

15.2. Determination of Sample Size

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. An additional 20 patients will be enrolled to support safety and efficacy

evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.

15.3. Pharmacokinetic Analyses

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, metabolite OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

PK analysis will based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.

15.4. Safety Analyses

Safety analyses will be conducted using the Safety population. Safety data, including AEs, vital signs, ECG, and clinical laboratory results will be summarized by treatment group using the Safety Population.

The incidence of TEAEs and SAEs will be tabulated by system organ class (SOC) and preferred term for each treatment group, and similarly by severity and relationship to treatment.

Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized.

CP scores will be summarized by treatment group at Baseline and at each post-Baseline visit.

No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.

15.4.1. Adverse Events

AEs will be coded using MedDRA. Summary tables of TEAEs will be provided.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs.
- Patient incidence of TEAEs and the total number of entries by MedDRA SOC and PT. This summary will be repeated for all subgroups.
- Patient incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Patient incidence of TEAEs by MedDRA SOC, PT, and closest relationship to investigational product (Related/Not Related). Related AEs are those with relationships reported as “Definite,” “Probable,” or “Possible,” and unrelated AEs are those with relationships reported as “Unlikely” or “Not Related.” At each level of

patient summarization, a patient is classified according to the closest relationship if the patient reported 1 or more events. AEs with a missing relationship will be considered related for this summary.

- Patient incidence of serious TEAEs and the total number of entries by MedDRA SOC and PT.
- Patient incidence of TEAEs leading to investigational product withdrawal or study discontinuation by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Patient Discontinued from Study" is checked.

The following listings will be presented by treatment group and patient:

- All adverse events.
- Serious adverse events (This is a subset of the AEs where serious is marked as "Yes").
- Severe adverse events (This is a subset of AEs where severity is marked as "Severe").
- Related adverse events (This is a subset of the AEs where relationship marked as "Definite," "Probable," or "Possible").
- Adverse events leading to Study Drug Withdrawal or Study Discontinuation (This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Patient Discontinued from Study" is checked).
- Adverse events leading to death (This is a subset of the AEs where the corresponding AE number is specified on the Death eCRF).

15.4.2. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.

Vital Signs and Weight

The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.

Electrocardiograms

Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.

15.4.3. Adverse Events of Special Interest

Pruritus: Treatment-emergent pruritus, defined as any preferred term including "Prur," will be summarized separately by the MedDRA SOC, treatment group, and PT as a subset of all TEAEs. This summary will be repeated for patients with "new or worsened" pruritus events, as defined as follows:

- Mild, moderate, or severe treatment-emergent pruritus events in patients with no pruritus at Baseline, or
- Worsening of the severity of the Baseline condition in patients with pruritus at Baseline.

Baseline pruritus is defined as the investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose Baseline severity is severe will be counted as worsening if an AE of pruritus with severe is recorded.

An analysis of treatment-emergent pruritus event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between pruritus and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent pruritus
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Patients who never reported an AE of pruritus will be censored at the date of last contact.
- Time to onset of the first moderate or severe treatment-emergent pruritus
  - The time to the start of the first moderate or severe pruritus will be calculated by date of onset of the first moderate or severe pruritus – date of first dose of investigational product +1.
  - Patients who never reported a moderate or severe AE of pruritus will be censored at the date of completion or discontinuation.
- Time to onset of the first severe treatment-emergent pruritus
  - The time to the start of the first severe pruritus will be calculated by date of onset of the first severe pruritus – date of first dose of investigational product +1.
  - Patients who never reported a severe AE of pruritus will be censored at the date of completion or discontinuation.

The analysis of time to first onset of treatment-emergent pruritus AE, time to onset of the first moderate or severe treatment-emergent pruritus, and onset of the first severe treatment-emergent pruritus will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without pruritus (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The tabulation will include the KM estimate methodology using 25th, 50th (median), and 75th percentiles of the medians and corresponding with associated 2-sided 95% confidence intervals (CIs), if the medians can be estimated as well as percentage of censored observations.

Fatigue: Treatment-emergent fatigue is defined as any preferred term which includes "Fatigue." New or worsened treatment-emergent fatigue is defined as follows:

- Any mild, moderate, or severe treatment-emergent fatigue events in patients with no fatigue at Baseline, or
- Worsening of the severity of the Baseline condition in patients with fatigue at Baseline.

Baseline fatigue is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose Baseline severity is severe will be counted as worsening if an AE of fatigue with severe is recorded.

An analysis of treatment-emergent fatigue event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between fatigue and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent fatigue
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Patients who never reported an AE of fatigue will be censored at the date of last contact.
- Time to onset of the first moderate or severe treatment-emergent fatigue
  - The time to the start of the first moderate or severe fatigue will be calculated by date of onset of the first moderate or severe fatigue – date of first dose of investigational product +1.
  - Patients who never reported a moderate or severe AE of fatigue will be censored at the date of last contact.
- Time to onset of the first severe treatment-emergent fatigue
  - The time to the start of the first severe fatigue will be calculated by date of onset of the first severe fatigue – date of first dose of investigational product +1.

- Patients who never reported a severe AE of fatigue will be censored at the data of last contact.

The analysis of time to first onset of treatment-emergent fatigue AE, time to onset of the first moderate or severe treatment-emergent fatigue, and onset of the first severe treatment-emergent fatigue will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without fatigue (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group.

15.5. Efficacy Analyses

This study does not plan to test a formal hypothesis for any efficacy endpoint.

The endpoints of efficacy assessments are change in total and direct bilirubin, INR, creatinine, albumin, platelets, ALP, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Summary statistics of the laboratory values will be provided by treatment group. The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 2-sided 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 2-sided 95% CI of the difference will also be presented.

Risk Scores: Changes from baseline in the MELD score and in CP score will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.

Shifts in MELD scores from Baseline will be reported by visit using the following categories: <10, 10 to <12, 12 to <13, 13 to <14, 14 to <15, and ≥15.

CP class will be presented in shift tables showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of patients within each shift classification.

Individual factors will be presented in a listing.

15.6. Additional Efficacy Analyses

Analyses of changes in liver stiffness and ELF, cytokeratin-and TIMP-1, and markers of inflammation will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin.

The following clinical endpoints will be captured in the study:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Time to variceal bleed
  - Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC) will be summarized by treatment group using the same methods as defined above.

15.7. Handling of Missing Data

Missing data will be assumed to be missing at random. No data will be imputed.

15.8. Data Monitoring Committee

An independent DMC includes hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), and statistician(s) not involved in the study as Investigators, adjudication committee members, or consultants. The DMC will have oversight of the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the Food and Drug Administration (FDA) debarment list will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data in order to ensure the safe and proper treatment of patients. Based on review of these data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study.

Written minutes of both the open and closed DMC sessions will be prepared. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked.

Data listings provided to the DMC do not contain individual patient treatment information; however, the DMC will have access to the database and may unblind individual patient data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all patients and separate treatment columns with 'dummy' labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.

The DMC may agree to adjust meeting frequency based upon actual and projected safety and efficacy data availability. Adjustments to or stopping of the protocol defined doses may be considered based on DMC evaluation of OCA safety and tolerability.

All Investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to patient safety, which alter the conduct of this study. The Investigators will inform the patients of such actions and the protocol, PIS, and ICF will be revised, as appropriate.

15.9. Adjudication Committees

All suspected liver-related clinical events, major adverse cardiovascular events (MACE)/expanded MACE, and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 3 committees and event types they are responsible for adjudicating are as follows:

- Cardiovascular Adjudication Committee (CAC): Adjudicates all suspected MACE, including all deaths

- Hepatic Outcomes Committee: Adjudicates all deaths and suspected liver-related outcomes
- Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events

Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the suspected events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual patient treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

Study records at each site will be monitored at regular intervals by a representative of the Sponsor, the CRA. The role of the CRA is to aid the Investigator in the maintenance and documentation of complete, accurate, legible, well organized and easily retrievable data. In addition, the CRA will ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such must be given access to the patient’s primary source documentation (eg, paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

The Investigator may exercise judgment in allowing the CRA access to particular sections of the patient's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

16.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IEC/IRB, and/or regulatory agencies to conduct one or more site audits during or after the study and agrees to allow access to all study-related documentation and information and be available for discussion about the study.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the Sponsor or designated personnel (eg, CRA), instruction manuals, data verification, cross checking, and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate collection of study data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the PIS-IC and/or other patient information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to Intercept before he or she can enroll any patient into the study. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to study patients to the IRB/IEC for review.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. A favorable opinion on amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/ IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of SARs will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or its designee will provide reports to the IRB/IEC as requested, as a minimum annually, and after the study is complete.

18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, "(64th World Medical Association [WMA] General Assembly, Fortaleza, Brazil, October 2013),"and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

18.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated consent form must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the patient.

18.4. Patient Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

The Investigator will maintain a list of patient's names and identifying information (eg, patient's hospital number, unique patient number). This list will not be collected by the Sponsor.

The PIS-IC will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique patient number/randomization code/site number, only.

When personal data on patients are stored or processed by computer, the data must be protected to prevent disclosure to unauthorized third parties. The pertinent sections of the data protection laws in the country in which the protocol is being conducted will be complied with in full.

The PIS-IC will explain that, for data verification purposes, authorized representatives of the Sponsor, regulatory authorities, or IEC/IRBs may require direct access to parts of the hospital or study site records relevant to the study, including patient's medical history.

19. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the patients for the duration of the study. If the Investigator is not present in the study site during the assessment, he or she will leave instructions for the study site staff and a telephone number where he or she can be reached.

Named physician(s) will be responsible for the medical follow-up of patients, as applicable.

19.1. Adverse Event Reporting

The Investigator is responsible for recording AEs reported by the patient or discovered by any other means during the study. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

19.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the Investigator considers a patient's safety to be compromised if immediate action is not taken.

19.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

- Approved PIS-IC (all versions)
- IRB/IEC approvals (of protocol/amendments, patient questionnaires, etc)
- Form FDA 1572
- Current medical license of Investigators
- Curriculum vitae of Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

19.4. Ethics Review (IRB/IEC)

Please see Section 18.1 for the Investigator's responsibilities regarding ethics review.

19.5. Archiving and Record Retention

The Investigator should retain all essential documents and correspondence relating to this study in the Investigator Site File (ISF). Any study documents stored elsewhere should have their location referenced in the ISF table of contents or in a note to file.

All documents relating to the study including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed study patient log and

confidential patient identification list will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor before the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

20. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include the following:

- Clinical Trial Registries (eg, www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (eg, basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions prior to the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data prior to the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the

costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.

- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
- Single Center Publication and Additional Publications: This is a multicenter study and is designed to be published with complete data from all the study sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter study and that the study was not intended, or statistically powered, for data presentation by a single study site.
- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this study to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and amendments, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

21. LIST OF REFERENCES

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APPENDIX A. SUMMARY OF CHANGES: PROTOCOL 747-401 VERSION 2 (DATED 22 MAY 2017)

Please note that Protocol 747 401 Version 1 was generated to specifically address US FDA post-marketing requirements but was not submitted to other Regulatory/Competent Authorities or Ethics Committees due to ongoing negotiations. The changes in Version 2 were incorporated based on FDA review of Version 1 of the protocol. In general:

- Background information was included to estimate the exposure difference between healthy subjects and patients with moderate hepatic impairment to support the rationale for dose selection (Section 5.4.2)
- Additional PK sampling times were added to adequately characterize the PK of OCA and its active metabolites at steady-state in patients with moderate and severe impairment when dosing weekly to biweekly (Section 12)
- The period between screening and Day 1 was extended to at least 14 days to establish a baseline for serum biomarkers with at least two samples two weeks apart (Schedule of Study Procedures, Section 9.7.4)
- The Week 3 contact Visit by email/telephone was changed to a Safety Visit to assess evidence of early hepatotoxicity (Schedule of Study Procedures, Section 9.7.6)
- Guidelines were added to assess patients for evidence of hepatotoxicity at each visit (Section 8.4.1.2).

The table below includes substantial revisions made to Protocol 747-401 under Version 2. Revised text in Version 2 is indicated in bold font, and the text deleted from Version 1 is crossed out in the table below. (Minor/editorial changes and non-substantial changes are not listed individually in the summary table below).

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Title Page	~~**(For FDA Review Only)**~~	**EudraCT Number: 2017-001762-13**	Added EudraCT Number
STUDY PERSONNEL CONTACT INFORMATION	~~**Emergency Contact Information**~~ **Medical Monitor - ~~24-hour Emergency Reporting~~** Contact: PPD MD, Medical Director, ~~Drug Safety,~~ Intercept Pharmaceuticals, Inc. ~~Mobile:~~ PPD	**Medical Monitor** **Primary** Contact: PPD MD, Medical Director, **PI** Intercept Pharmaceuticals, Inc. (Intercept) Telephone: PPD Email: PPD	Updated contact list.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	Telephone: PPD Email: PPD ~~**Or if Not Available:**~~ ~~Contact:~~ PPD ~~MD, PhD, Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~**SAE Contact Information**~~ ~~SAE Fax:~~ PPD ~~SAE email address~~ PPD ~~Telephone~~ PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD ~~VP, Clinical Operations, Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~Mobile:~~ PPD ~~Fax:~~ PPD ~~Email:~~ PPD	SAE Fax: PPD SAE Email: PPD	
Synopsis, Investigators	The study is planned to have approximately ~~20~~ investigational sites, globally	The study is planned to have approximately **35** investigational sites, globally	Updated site numbers.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
and/or Study Center(s)			
Synopsis, Study Period, 7.1.3, Study Duration	Studied Period: The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete the primary treatment period at which point all patients will transition to an open-label long-term safety extension (LTSE).	Study Period: **Patients** will **receive double-blind treatment for at least** 48 **weeks. Patients who have completed their 48-**week **double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week** treatment period and the **database for** that period **is locked (approximately 3 years)**. Patients will **then be given the option** to **go on** open-label **treatment**.	Updated description of study period.
Synopsis, Objectives 6.1 Primary Objectives; 6.2 Secondary Objectives, 6.3, Additional Objectives,	: In patients with Moderate to Severe PBC: • To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and OCA glucuronide – Liver biochemistry including total bilirubin – … aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT – – Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF 19), 7α hydroxy-4-cholesten-3-one (C4), and plasma and fecal bile acids • To assess the PK/Pharmacodynamic (PD) relationship of OCA on: ` ALP, total bilirubin, and aminotransferases ` Bile acid homeostasis ` Safety and tolerability (eg pruritus)	• To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and **metabolite** OCA glucuronide **compared with placebo** – Liver biochemistry including total **and direct** bilirubin – … aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT],), **international normalized ratio (INR), creatinine, albumin, platelets** – Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF 19), 7α hydroxy-4-cholesten-3-one (C4), and plasma bile acids • To assess the PK/Pharmacodynamic (PD) relationship of OCA with: ` **PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)**	Clarified study objectives.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	• To assess clinical ~~outcomes~~ consistent with end-stage liver disease	• **To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ])** • To assess clinical **events** consistent with end-stage liver disease	
Synopsis, Methodology and Section 7.1. Overall Study Design	Patients will be screened ~~for up to~~ ≤14 days…	Patients will be screened **≥14 days but not more than 28 days**…	Extended to 14 days to satisfy PMR for 2 baseline measurements.
Synopsis, Double-Blind Treatment Period, 7.1, Overall Study Design	Double-Blind ~~Primary~~ Treatment Period … (ie, Day 1 through Week 48), clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, ~~PK~~, and PD ~~(trough)~~. At each visit, ~~trough~~ PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12 ~~and only after a patient uptitrates~~. ~~Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the 48-week primary treatment period~~.	… Double-Blind Treatment Period: …(ie, Day 1 through Week 48), **an initial safety visit will occur at Week 3. After the Week 6, subsequent** clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. At each visit **(except screening and Week 3)**, **fasting** PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12, **18, 24, 30, and 48.** **Patients who have completed their 48-week double-blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. Patients will then be given the option to go on open-label treatment.**	Updated description of study period.
Synopsis, Long-term Open Label Extension Phase	~~Long-term Open Label Extension Phase~~ ~~Once all patients have completed the double-blind 48-week primary treatment period, patients will have the option to continue into an open-label long-term safety extension and all patients will receive OCA. Visits in the LTSE will occur every 3 months for up to 5 years. Patients on placebo during the primary treatment period will initiate study medication at 5-mg OCA once weekly and follow the dosing regimen based on their CP score. Patients on OCA~~	Section deleted.	Updated description of study.

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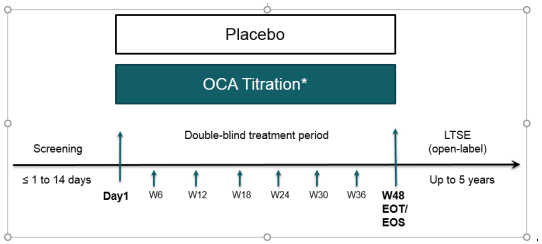
	~~during the primary treatment period will continue the dose that they are on once unblinded.~~		
Synopsis and Section 7.1.1, Study Design Diagram	 ~~EOS = end of study; EOT = end of treatment,~~ OCA = obeticholic acid *Initial dose titration of investigational product ~~may occur at the Week 12 Visit, or any study visit~~ …	 **Note:** Initial dose titration of investigational product may **be considered as early as the Week 12 visit**, or any study visit thereafter for patients on all dosing regimens, based on …. **Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.**	Updated study diagram.
Synopsis, Dosing Regimen, Section, 7.3 (Table 2)	All patients will initiate investigational product once weekly with 5 -mg OCA or matching placebo. ~~Starting~~ at Week 12, ~~safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below:~~ • ~~At Week 12~~, if investigational product is tolerated and laboratory assessments ~~from the Week 6 visit~~ do not indicate a safety concern, the patient ~~will change the dosing frequency~~ to 5 mg twice weekly, at least 3 days apart. • ~~Following an additional~~ 6 weeks ~~of treatment, if investigational product is tolerated,~~ patients ~~may be up-titrated to OCA~~ 10 mg twice weekly at least 3 days apart, the maximum dose for patients with CP-C. • Following an additional 6 weeks of treatment, if tolerated, Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, the maximum dose for patients with CP-B.	All patients will initiate investigational product once weekly with 5 mg OCA or matching placebo. **Titration may be considered as early as the Week 12 Visit. Following visit procedures** at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient **may up-titrate to OCA 5** mg twice weekly **and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur** at least 3 days apart. **Every** 6 weeks **thereafter, based on safety and tolerability assessments**, patients **can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.** Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily. **Patients with CP-C may titrate to a maximum dose of OCA** 10 mg twice weekly at least 3 days apart.	Updated table for clarity.

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr>
<td></td>
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• ~~If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply.~~

Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score
<table>
<tr><td></td><td colspan="2">Child-Pugh B
(Moderate Hepatic Impairment)</td><td colspan="2">Child-Pugh C
(Severe Hepatic Impairment)</td></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose [a] (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>5 mg once weekly</td><td>matching placebo</td></tr>
<tr><td>Titration 1[b] ~~(≥Week 12)~~</td><td>5 mg twice weekly[c]</td><td>matching placebo</td><td>5 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 2[b] ~~(≥6 weeks after Titration 1)~~</td><td>10 mg twice weekly[c]</td><td>matching placebo</td><td>10 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 3[b] ~~(≥6 weeks after Titration 2)~~</td><td>5 mg once daily</td><td>matching placebo</td><td>NA</td><td>~~matching placebo~~</td></tr>
</table>
~~[a]Starting dose based on patient's Child-Pugh Score at Screening.~~
[b]Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.
[e]Dosing per the twice weekly schedule must be at least 3 days apart.
</td>
<td>
<table>
<tr><td></td><td colspan="2">Child-Pugh B
(Moderate Hepatic Impairment)</td><td colspan="2">Child-Pugh C
(Severe Hepatic Impairment)</td></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>5 mg once weekly</td><td>matching placebo</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo</td><td>5 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo</td><td>10 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 3[a]</td><td>5 mg once daily</td><td>matching placebo</td><td>NA</td><td>NA</td></tr>
</table>
[a]Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study
[b]Dosing per the twice weekly schedule must be at least 3 days apart.
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td></td><td>(insertion)</td><td>If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply. If a patient demonstrates an improvement to CP-A, they should follow the dosing regimen for patients with CP-A.

Over the course of the study, a patient’s CP category may change. When a patient demonstrates a change in CP category, dosing should be reassessed and modified if appropriate. Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply. If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen should be followed.

Maximum Dose for OCA or Matching Placebo for Changes in Child-Pugh Category
<table><tr><th rowspan="2">Original Status</th><th colspan="3">New Status[a]</th></tr><tr><th>Child-Pugh A</th><th>Child-Pugh B</th><th>Child-Pugh C</th></tr><tr><td>Child-Pugh B</td><td>No change</td><td>No change</td><td>10 mg twice weekly[b]</td></tr><tr><td>Child-Pugh C</td><td>5 mg once daily</td><td>5 mg once daily</td><td>No change</td></tr></table>
[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for the planned dosing regimen.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.</td><td>Added to provide more information on dosing.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Synopsis and Section 8.2, Key Inclusion Criteria	2. Evidence of cirrhosis including at least one of the following: ` Biopsy ~~indicating cirrhosis or a medical history with histological evidence of cirrhosis~~ ` Clinical evidence consistent with cirrhosis including: ~~esophageal~~ varices, ascites, ~~encephalopathy,~~ or portal ~~hypertension~~ ` Liver stiffness as assessed by TE of ~~≥~~16.9kPa 6. ~~Age ≥18 years~~ 7. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate UDCA (no UDCA for ≥3 months) 8. ~~Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:~~ – ~~Barrier method, ie, (a) condom (male or female) with spermicide **or** (b) diaphragm, with spermicide; or~~ – ~~Intrauterine device; or~~	2. Evidence of cirrhosis including at least one of the following: • Biopsy **results consistent with PBC Stage 4** • Liver stiffness as assessed by TE **Median Value** ≥16.9 kPa • Clinical evidence **in the absence of acute liver failure** consistent with cirrhosis including: **gastroesophageal** varices, ascites, **radiological evidence of cirrhosis (nodular liver or enlargement** of portal **vein and splenomegaly)** • **Combined low platelet count (<140 000/mm^3) with** – **persistent decrease in serum albumin, or** – **elevation in prothrombin time/INR (not due to antithrombotic agent use), or** – **elevated bilirubin (2× ULN)** 6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate **or unresponsive to** UDCA (no UDCA for ≥3 months)	Provided more details regarding inclusion requirements. Only listed inclusions directly related to PBC in synopsis. Other criteria were deleted from synopsis but remain in the main body. Only criteria with changes are presented in this SOC. The full inclusion/ exclusion list is in the body of the protocol.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	– ~~Vasectomy (partner), or~~ – ~~Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection, or~~ – ~~Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)~~ 9. ~~Must provide written informed consent and agree to comply with the study protocol.~~		
Synopsis and Section 8.3, Key Exclusion Criteria	4. History or presence …: – Hepatitis C virus infection RNA positive 5. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function~~ during the Screening period~~ 6. ~~Patients with history or presence of hepatorenal or hepatopulmonary syndrome~~ 7. ~~Patients with significant active infection (ie spontaneous bacterial peritonitis)~~ 8. ~~Patients with known or suspected hepatocellular carcinoma~~ 9. ~~History of known or suspected clinically significant hypersensitivity to OCA or any of its components~~ 10. ~~Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study~~	4. **Hepatic encephalopathy (as defined by a West Haven score of ≥2)** 5. History or presence …: – Hepatitis C virus infection **and** RNA positive 6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function~~-~~**prior to randomization**	Added additional **key** exclusion criteria #4. Other criteria were deleted from synopsis but remain in the main body. Only criteria with changes are presented in this SOC.

Section	Original Text (Version 1, 20 Dec 2016)		Revised Text (Version 2, 22 May 2017)		Key Change
	11. ~~Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain~~ 12. ~~UDCA naïve (unless contraindicated).~~				
Synopsis, Duration of Treatment	~~The study will include a 14-day screening period and a 48 week double-blind primary treatment period. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the double-blind 48-week primary treatment period. Hence, depending on the rate of patient enrollment, patients will be exposed to investigational product for a minimum of 1 year up to approximately 2 years during the blinded period. Following completion of the blinded period, Patients will have the option to continue into an extension during which they will receive open label treatment and be seen at regular visits every 3 months for up to 5 years.~~		**Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment.**		Updated description of study.
Synopsis, Criteria for Evaluation and 11, Overview of Assessments, Table 5, Additional Objectives	~~PD Parameters;~~	plasma, ~~fecal~~ bile acids	**PK**	**Plasma concentrations of OCA and its conjugates, glyco-OCA, tauro-OCA; and metabolite OCA glucuronide**	Clarified study parameter for evaluation.
	Changes in MELD and in CP score		Changes in MELD and in CP score **and components of the CP score**		

Section	Original Text (Version 1, 20 Dec 2016)		Revised Text (Version 2, 22 May 2017)		Key Change
	PD parameters	f~~ecal~~ bile acids	**PK**/PD parameters	bile acids	
	Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30, ~~and others as determined during course of study.~~		IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30,	
	~~PK/PD relationship of OCA and liver biochemistry~~	~~OCA and its conjugates, glyco-OCA tauro-OCA; and OCA glucuronide~~	PK/PD relationship	**PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)**	
	~~PK/PD relationship of OCA and bile acid homeostasis~~	~~Bile acids~~			

Section	Original Text (Version 1, 20 Dec 2016)		Revised Text (Version 2, 22 May 2017)		Key Change
	Clinical ~~Outcomes~~	Incidence and time to first occurrence of any of the following: all-cause mortality, liver-related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, ~~hepatocellular carcinoma~~	Clinical **Events**	Death (all-cause and liver-related), liver transplant, Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline), Hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, Uncontrolled ascites, and HCC.	
Synopsis, Statistical Methods, Safety Analyses	The absolute change from baseline will also be summarized. No inferential comparison ~~of safety endpoints~~ will be performed.		The absolute change from baseline will also be summarized. No inferential comparison **with formal statistical hypothesis testing** will be performed **for safety endpoints.**		Clarified statistical methods.
Synopsis, Statistical Methods, Additional Efficacy Analyses	The following clinical ~~outcomes~~ will be captured in the study: • ~~All~~ cause ~~mortality~~ • Liver related death • Liver transplant		The following **endpoints consistent with end-stage liver disease** will be captured in the study: • **Time to death** (all cause) • **Time to** liver-related death • **Time to** liver transplant		Clarified statistical methods.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	• Variceal bleed • Hepatic encephalopathy • Bacterial peritonitis • ~~Ascites~~ • ~~Hepatocellular carcinoma~~ The incidence and time to first occurrence of any of the above listed clinical outcomes will be summarized ….The tabulation will include the KM ~~estimate of the medians~~ and corresponding 95% confidence intervals (CIs), ~~if the medians can be estimated~~. … The hazard ratio and 95% CI will be estimated based on a Cox regression model stratified by randomization strata. In addition, the incidence and time to each of the above ~~outcomes~~ -will be summarized by treatment group using the same methods as defined above.	• **Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)** • **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:** – **Time to** variceal bleed – **Time to** hepatic encephalopathy **(as defined by a West Haven score of ≥2)** – **Time to spontaneous** bacterial peritonitis **(confirmed by diagnostic paracentesis)** • **Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)** The incidence and time to first occurrence of the above listed clinical outcomes will be summarized ….The tabulation will include the KM **methodology using 25th, 50th (median),** and **75th percentiles with associated 2-sided** 95% confidence intervals (CIs), **as well as percentage of censored observations**. …. The hazard ratio and **2-sided** 95% CI will be estimated based on a Cox regression model stratified by randomization strata. In addition, the incidence and time to each of the above **clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC)** will be summarized by treatment group using the same methods as defined above.	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Synopsis and Section 15.2, Sample Size,	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients per OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. ~~The assessment was based on 80% powering for the 90% confidence interval of the geometric mean ratio of Total OCA (sum of OCA, glyco-OCA, and tauro-OCA).~~	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. **An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.**	
5.2, Nonclinical Experience with Obeticholic Acid	Insertion	**Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.**	Added section to briefly address nonclinical studies.
5.3, Clinical Development of Obeticholic Acid	As of 31 Jan 201~~6~~, approximately ~~1726~~ patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ patients had PBC, ~~330~~ patients had nonalcoholic steatohepatitis, 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease, 33 patients had alcoholic cirrhosis/portal hypertension, ~~and~~ ~~20~~ patients had primary sclerosing cholangitis (PSC).	As of 31 Jan 201**7**, approximately **2186** patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** patients had PBC, **686** patients had nonalcoholic steatohepatitis (**NASH**), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (**NAFLD**), 33 patients had alcoholic cirrhosis/portal hypertension**,** **52** patients had primary sclerosing cholangitis (PSC), **and 5 patients had biliary atresia.**	Updated numbers of patients who have received OCA.
5.4, Rationale for Study Design and Dose for Investigational Product		**5.4 Rationale for Study Design and Dose for Investigational Product**	Inserted new header for clarity
5.4.1, Rationale for Study Design	~~Patients with moderate or severe hepatic impairment (Child Pugh B or C) will constitute approximately 20% of the patients included in the ongoing clinical outcomes Study 747-302 which was~~ specifically designed to confirm clinical benefit across the spectrum of disease including patients	**The 747-401 study is** specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment**.** Data collected from Study 747 401 will serve as a bridge to the **747-302 study.**	Clarified the intent of the 401 study.

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	with hepatic impairment. Data collected from Study 747 401 will serve as a bridge ~~between~~ the ~~two studies.~~		
5.4.2, Rationale for Obeticholic Acid Dose and Duration	~~Results from the hepatic impairment study (747-103) indicate that plasma exposure increases, in comparison to subjects with normal liver function, with increasing severity of impairment as classified by Child Pugh A (CP A), CP B or Child Pugh C (CP C) scores by 1.4 , 8.0 , and 13 fold, respectively. No apparent impact on the overall safety profiles were observed in this study. Liver exposure, however, modestly increased by 1.1 , 1.5, and 1.7 fold, respectively, as shown in simulations using a physiologic PK model developed to characterize OCA and its conjugates.~~ Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure. (insertion)	**Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (CP Score). Model simulations predicted that for mild (Child-Pugh A [CP-A]), moderate (Child-Pugh B [CP-B]), and severe (Child-Pugh C [CP-C]) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to patients with normal hepatic function, whereas total OCA liver concentrations increase 1.1-, 1.5-, and 1.7-fold, respectively. Because the liver is the primary site of action for the safety and efficacy of OCA, it is important to account for the differences in systemic and liver exposure when assessing effective doses. It is also important to note that while hepatically impaired (CP-B and C) patients treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy patients, no apparent impact on the overall safety profile was observed, consistent with only a modest increase in liver exposure of OCA associated with hepatic impairment. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.** **Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower**	Added rationale for OCA dosing in hepatically impaired patients.

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	Therefore, a modified dosing regimen is recommended for OCA in patients with moderate and severe hepatic impairment that is designed to initiate doses to achieve plasma exposures levels of OCA similar to those without hepatic impairment or CP-A. After which, subjects may then titrate their doses upwards to achieve liver exposures that would be similar in both patient populations. ~~This modified dosing regimen was selected based on the established safety and tolerability of OCA in subjects with PBC, along with PK/PD modeling and simulations. Patients will initiate dosing at OCA 5 mg once weekly. Starting at Week 12, if the prior dose regimen was tolerated, the patients will increase the dosing frequency to 5 mg twice weekly (at least 3 days apart). After 6 weeks, a second titration may occur to OCA 10 mg twice weekly as long as tolerated. Patients classified as CP-B may further titrate their dose upwards to OCA 5 mg once daily after 6 weeks on the OCA 10 mg twice weekly regimen.~~	**dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).** **The dosing regimen in this study follows the FDA-approved prescribing information, with the exception of the maximum allowed dose in patients with moderate impairment. While the prescribing information allows for a maximum dose of 10 mg twice weekly for patients with moderate impairment, the protocol allows for a maximum dose of 5 mg once daily. The choice of 5 mg once daily is supported by the estimated steady-state liver and plasma exposure of total OCA for patients with moderate hepatic impairment receiving a 5 mg once daily dose relative to healthy patients receiving a 10 mg dose. A maximum allowed dose of 5 mg once daily in patients with moderate hepatic impairment is estimated to achieve liver exposure similar to non-hepatically impaired patients receiving a 10 mg daily dose and maximize efficacy in this patient population.**	
7.1.2, Schedule of Study Procedures	Schedule of Study Procedures ~~(Double-Blind Treatment Period)~~	Schedule of Study Procedures	Updated procedures to match updated study design.
7.1.2, Schedule of Study Procedures, Visit Windows	~~≤ 1~~ to -14 days	**-28** to -14 days	Updated procedures to match updated study design.
7.1.2, Schedule of Study Procedures, Visit Weeks Row	Week 3: ~~Safety Contact~~ Week 48 Under Long-Term Treatment	Week 3 Week 48/**ET/EOS/EOT** **Every 3 months**	Week 3 telephone/email contact visit now a

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			laboratory safety visit.
7.1.2, Schedule of Study Procedures	(Insertion) Dose Titration IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30, ~~others as determined during course of study~~ ~~Fecal PK Analysis~~ ~~TE Fibroscan®~~ ELF ~~MELD~~ PK ~~trough~~ Collection	Column: **Long-Term Treatment** Procedures: **Medical and Surgical Procedures** Dose Titration **Assessment** **Markers of Inflammation:** IL-6, hs CRP, TNF-α, IgM, IgG, IgA, CK-18-M30 • **TE**/ELF **(HA, P3NP, and TIMP 1)** PK **Fasting** Collection	Updated procedures to match updated study design
7.1.2, Table 1, Schedule of Study Procedures Footnotes	~~a~~ Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 3 and continuing to Week 48 to assess for AEs, concomitant medications, and verify that s/he is dosing as directed. b ~~Visits should be based on Day 1.~~ ~~c~~ The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits ~~(except Screening Visit 1)~~ but water is permitted. ~~d Medical history performed at Screening only.~~ ~~e The yearly physical exam will also include an~~ assessment of smoking and alcohol consumption history and current habits ~~for both~~. ~~Height~~ will ~~only~~ be collected at Day 1 and Week 48. ~~f~~ Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF. ~~g~~ The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated	**aVisit schedule should be based on Day 1. Day 1 visit must occur at least 2 weeks after screening visit.** [b]**Patients** should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week **9** and continuing to Week 48 to assess for AEs, concomitant medications, **medical/surgical procedures**, and verify that s/he is dosing as directed. [c] **Preferably, the patient comes in to the clinic for this visit. Alternatively, site will telephone the patient for assessments and home health nurse will visit to draw safety labs.** [d] **Visit should occur 3, 4, or 5 days after taking the Week 6 dose.** **e** The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, **including screening**, but water is permitted. f **Height and** assessment of smoking and alcohol consumption history and current habits will be **assessed** at **Screening** and Week 48. **Assessment of smoking and**	Updated procedures to match updated study design

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	translation is not available in the local language required for a specific study patient, the ~~data from that~~ questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease. ~~h~~ Patients will be instructed to begin dosing on the Day 1 visit after completing all study assessments. ~~(ie, on Day 1~~). Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet. ~~i~~ ~~Initial~~ dose titration of investigational product may occur at the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score. j Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally)	**alcohol consumption history and current habits will be assessed quarterly after Week 48.** g Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF. h The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease. **i New investigational product bottles will be dispensed if the patient is titrated. Unless up-titrated, patients are expected to use up each investigational product bottle before a new bottle will be dispensed. No new bottles will be dispensed if dose frequency is changed**. Patients will be instructed to begin dosing **on Day 1**, after completing all study assessments. Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet. **j** Dose titration of investigational product may occur starting **after the** Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score. **k** Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit **(except Week 3**). If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally).	

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		l The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling. **m The noninvasive radiological liver fibrosis measurement devices (such as, FibroScan® device [Echosens; Paris, France]) will be used at all study sites to collect hepatic stiffness measurements.** **n Patients will complete a TE/ELF and ultrasound assessment, every 6 months (±2 weeks) after Week 48.** **o ECG and urine dipstick will be done yearly (±2 weeks) after Week 48 Visit.** **p Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm suspected HCC.**	
7.1.3, Study Duration	~~The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the primary treatment period, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete the primary treatment period (Figure 1). Patients will have the option to continue into an open-label LTSE after all patients have completed the Week 48 procedures in which they will receive open-label treatment and be seen at regular visits every 3 months for up to 5 years.~~	**Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment**.	Updated description of study period.

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7.3, Planned Dosing Regimen	All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. ~~Starting~~ at Week 12, ~~safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below (Table 2):~~ • ~~At Week 12,~~ if investigational product is tolerated and laboratory assessments ~~from the Week 6 visit~~ do not indicate a safety concern, the patient will ~~change the dosing frequency to~~ 5 mg twice weekly, at least 3 days apart. ~~Following an additional 6 weeks of treatment, if investigational product is tolerated, patients may be up titrated to OCA~~ 10 mg twice weekly at least 3 days apart, ~~the maximum dose for patients with CP-C~~ ~~Following an additional~~ 6 weeks ~~of treatment, if tolerated~~, patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, ~~the maximum dose for patients with CP-B~~.	All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. **Titration may be considered as early as the Week 12 visit. Following visit procedures at** Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient will **up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur** at least 3 days apart**. Every 6 weeks thereafter, based on safety and tolerability assessments, patients can be considered for further up titration as described below (Table 3). At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.** **Patients with CP-C** may titrate **to a maximum dose of** OCA 10 mg twice weekly at least 3 days apart. Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.	Clarified dosing regimen.
7.4, Dose Adjustment Criteria, Scheduled Dose Titration	~~The first dose titration for any patient may occur no earlier than 12 weeks following~~ initiation of OCA or matching placebo.	**After** initiation of OCA or matching placebo, **titration may be considered as early as the Week 12 visit.**	Clarified dosing regimen.
7.4.1, Pre-Titration Tolerability Assessment Requirements	Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. ~~A review of AEs and available safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within approximately 6 weeks of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigational product (eg, Week 6, laboratory results should be reviewed prior to titration at Week 12). If for any reason, laboratory results are not available at the time of the~~	Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. **To determine if a patient is eligible for a dose up-titration refer to Section 7.3**	Clarified dosing regimen.

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	~~planned up titration visit, additional laboratory samples must be obtained and reviewed, prior to up titrating the patient to a higher dose. 7.3~~ ~~To be eligible for a dose up-titration, patients should not be experiencing significant AEs that are suspected to be related to investigational product (eg, severe pruritus) or displaying other symptoms that may indicate intolerability of investigational product.~~		
7.4.2., Safety Criteria for Adjustment or Stopping Doses	~~Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.~~ ~~Subjects who discontinue investigational product are expected to continue in the study (and follow the regular visit schedule) until the end of the study, and the study will only terminate at the time.~~		This information has been incorporated into Section 8.4, which was renamed 8.4. Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study and additional text was added.
8.4, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	8.4 ~~Patient~~ Withdrawal ~~Criteria~~ (Insertion)	**Dose Adjustment, Interruption, and** Withdrawal **from Investigational Product or Study** **Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.**	Section revised to integrate withdrawal criteria in one section of protocol. Text was

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		Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling, but may withdraw consent at any time.	previously in Section 7.4.2.
8.4.1. Reasons for Additional Monitoring or Mandatory Interruption of Investigational Produc	8.4.~~1~~. Reasons for Mandatory Discontinuation of Investigational Product	Moved to 8.4.**2** 8.4.1. Reasons **for Additional Monitoring** or Mandatory Interruption of Investigational Product	Heading text updated.
8.4.1.1, Reasons for Additional Monitoring Related to Liver Chemistries	8.4.1.1. ~~Pregnancy~~	8.4.1.1. **Reasons for Additional Monitoring Related to Liver Chemistries** **Patients who develop ALT or AST >2x baseline (and >ULN) or total bilirubin >1.5x baseline (and >ULN) should have repeat testing within 48 to 72 hours to confirm values. Patients with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or INR with persistent increases in ALT or AST should also be closely monitored.**	Pregnancy moved to Section 8.4.1.3. New Section with text added.
8.4.1.2. Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	(Insertion)	8.4.1.2. **Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries** **Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3× baseline (and >ULN)** • **Total bilirubin >2× baseline (and >ULN)** **Repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing should be performed. Detailed adverse event information should also be collected, and the patient should be investigated for possible causes of the liver chemistry changes, as appropriate. The Investigator**	New Section added to meet PMR requirements.

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		should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable. **If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), patients should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms.** **For the purposes of this protocol, if the above referenced significant elevation in liver enzyme or bilirubin levels resolve following interruption of investigational product and no other cause for the elevation is identified, the elevations should be assumed to be related to investigational product and investigational product should be discontinued. If the liver enzyme or bilirubin levels do not resolve following interruption of investigational product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the patient may be re-challenged following a discussion between the Investigator or designee and the Sponsor.** **Elevation of liver enzymes or bilirubin is based on comparison to baseline values defined as the mean of all available Screening and Day 0 values, which are the mean of all available evaluations prior to the first administration of investigational product. At least 2 of these samples will be obtained a minimum of 2 weeks apart during the Screening period. Elevations that occur gradually over the course of the study may be indicative of disease progression and should be assessed as clinically appropriate. Liver enzyme and bilirubin elevations that occur over a shorter time, such as within a 6-month period, should be evaluated for drug-induced liver injury as provided in the guidelines below.**	

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		If at any time a patient develops signs or symptoms of hepatotoxicity such as new onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>7%) in combination with elevations in liver enzymes, investigational product should be interrupted and liver enzymes monitored until signs or symptoms resolve. **Patients who develop evidence of severe drug-induced liver injury that is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged. Severe drug-induced liver injury includes, but is not limited to, functional hepatic impairment, as indicated by rising bilirubin or INR that cannot be explained by progression of disease. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.** **If after all investigations and actions outlined above have been completed, the investigator determines that the elevations in liver biochemistries are considered not related to investigational product, the Sponsor must be contacted before investigational product can be reinitiated. Follow-up procedures for patients resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment. Results must be reported to the site as soon as possible so the Investigator can determine if it appropriate for the patient is to continue treatment.** **The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.** **All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 15.9)**	

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8.4.1.3, Pregnancy	(Insertion) ~~Whenever the site is notified of a possible pregnancy, the patient should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female patient becomes pregnant, the patient must stop taking investigational product immediately and be withdrawn from the study~~…	8.4.1.3. **Pregnancy** **If a female patient becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 13.1.10 pregnancy is not considered an AE for reporting purposes. The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 13.1.10). New baseline procedures should include pregnancy testing**.	Was Section 8.4.1.1
8.4.2, Reasons for Mandatory Discontinuation of Investigational Product	8.4.2. ~~Other Reasons for Discontinuation of Investigational Product or Study Termination~~	8.4.2. Reasons for Mandatory Discontinuation of Investigational Product **Patients who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these patients should be encouraged to consent to the semiannual telephone contact and/or continued record review only to allow for secondary outcome events data to be collected.**	Now Section 8.4.3 and text added.
	~~8.4.2.3. Elevated Liver Enzymes~~	Section deleted.	Information in 8.4.1.2 now covers this.
8.4.3, Other Reasons for Discontinuation of Investigational Product or Study Termination	~~Subjects who discontinue investigational product are expected to continue in the study until the end of the study or at the discretion of the Sponsor. If a patient experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe.~~ ~~Early termination procedures should only be conducted if the patient withdraws consent (See Section 9.7.14).~~	8.4.3. **Other Reasons for Discontinuation of Investigational Product or Study Termination** The following events are considered appropriate reasons for **a patient to discontinue investigational product; however, these patients are expected to continue in the study until study termination (or at the discretion of the Sponsor):** • **Patient begins treatment with commercially available OCA.** • **The Investigator or Sponsor considers that it is advisable or in the best interest of the patient.**	Was Section 8.4.2 and additional text added.

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	~~It is agreed that, for reasonable cause, either the Investigator or the Sponsor, may terminate this study.~~ ~~The following events are considered appropriate reasons for a subject to discontinue from the study:~~	• **The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to study drug.** • **Withdrawal of consent** – **Consent may be fully withdrawn (in which case the patient discontinues both investigational product and study visits and procedures).** – **Consent may be modified to discontinue study visits but allow semi-annual telephone contact.** – **Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE) and liver-related clinical outcomes.** – **Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.12)**	
8.4.3.1. Withdrawal of Consent to Continue in the Study	8.4.3.1. Withdrawal of Consent … their consent to continue in the study at any time (Insertion) A reasonable effort must be made to…	**8.4.3.1. Withdrawal of Consent to Continue in the Study** **Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.12).**	Added more information regarding withdrawal from study.
8.4.3.2. Lost to Follow-Up	8.4.2.2. Lost to Follow-Up ~~If a patient fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the patient, he or she~~ will be ~~withdrawn from the study~~.	**8.4.3.2. Lost to Follow-Up** **Patients** will be **considered "lost to follow up" only after documented attempts to reach the patient prove unsuccessful.**	Updated text.
8.4.4, Patient Discontinuation Notification	8.4.~~3~~. Patient Discontinuation Notification The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the	8.4.**4**. Patient Discontinuation Notification The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s)	Clarified text.

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	primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. ~~Patients will be considered "lost to follow up" only after reasonable, documented attempts to reach the patient prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a patient fails to return for required study visits or discontinues from the study.~~ This information must be documented in the eCRF.	for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. This information must be documented in the eCRF.	
9.2, Concomitant Medications	~~Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section) during the study.~~ Concomitant medications will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). … taken ~~prior to (ie~~, within 30 days of Screening~~)~~ and … Concomitant medications should be stable prior to Day 1 ~~(ie no change in dosing within 3 months of screening).~~	Concomitant medications (**other than prohibited concomitant medications listed in Section 9.2.2**) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). … taken within 30 days of Screening and during the study must be recorded in the source documents and … Concomitant medications should be stable prior to Day 1.	Clarified use of concomitant meds**.**
9.2.1, Drug Interactions	~~Patients taking~~ bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be ~~instructed to stagger their dosing~~ of investigational product and UDCA, ~~ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (and UDCA;~~ ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration).	Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should **not** be **taken within 4 hours** of **taking investigational product (**and UDCA **if applicable),** ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration)**.**	Clarified use of concomitant meds.
9.2.2, Prohibited Medications	Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.~~2~~). ~~Fibric acid derivatives (fibrates) and other medication intended to lower blood triglyceride levels are also prohibited while on investigational product.)~~	Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.**3**).	Some patient may be expected to be on fibrates.
9.4.2, Blinding	The patients, Investigator, and study site staff will be blinded to…	The **Sponsor**, patients, Investigator, and study site staff will be blinded to…	

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9.6, Restrictions	Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited.	Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited. **Previous exposure to OCA (as a study participant or received commercial OCA therapy) is allowed within 3 months prior to enrollment in this study**	Updated to include patients who may be on prescribed OCA and who received investigational OCA as study participants.
9.7.1, Visit Procedures	(Insertion)	**Visit windows are specified in the Schedule of Study Procedures (Table 1).**	Added text pointing to visit windows for study procedures.
9.7.2, Informed Consent Procedures	…The patient must be willing and able to provide written informed consent (on hard copies ~~or on electronic devices such as iPads)~~ before entering the study.	The patient must be willing and able to provide written informed consent (on hard copies) before entering the study.	Updated language.
9.7.3, Assessing Cirrhosis	~~To determine which dosing regimen patients should follow, cirrhosis should be assessed by the Investigator at Screening Visit 1.~~ Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators: – varices ~~Patients will be dosed according to their CP Score calculated in the eCRF (see Section 14.1.1 and Table 12).~~ ~~Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in cirrhosis status will necessitate re-evaluation of the dosing regimen.~~	Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators: – **Gastroesophageal** varices	Clarified assessment instructions.

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9.7.4, Screening Procedures	Screening Procedures ~~(1 day to~~ 14 days prior to Day 1)	Screening Procedures (14 days **to 28 days** prior to Day 1)	Updated procedures to match updated protocol design.
	The Screening Visit assessments must be performed ~~within~~ ≤14 days prior to Day 1 to…	The Screening Visit assessments must be performed ≥14 days prior to Day 1 to…	
	The patient is to review and sign the ICF	• **Verify that the patient has fasted for at least 8 hours.** – **Record fasting status in the source and eCRF** – **If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits**	
	~~• Obtain blood samples for serum chemistry, hematology, and coagulation tests.~~		
	• Perform a physical examination.	Perform a physical examination, **including smoking and alcohol consumption history, and current habits for both.**	
	(Insertion)	• **Record the visit in IWRS**	
	• Perform TE using the Fibroscan® TE device. ~~If TE has been done within 3 months of Day 1 and a report/adequate data are available, a pretreatment TE at Day 1 is not required.~~ If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	• Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	

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	~~• Provide kits and instructions for collection of stool specimens at home prior to the Day 1 visit~~	• Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required. If the ultrasound cannot be performed at Screening (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed anytime within the screening visit window or on Day 0. Results from the screening ultrasound should be reviewed to assess possible exclusion criteria prior to randomization.	Clarified sampling procedures.
9.7.5, Day 1 Procedures	` ~~Obtain blood samples for~~ markers of inflammation ` ~~ELF (including~~ HA, P3NP, and TIMP-1) ` ~~Trough~~ PK assessment	Markers of inflammation and fibrosis (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK -8-M30, HA, P3NP, and TIMP 1) **Fasting** PK assessment	Clarified sampling procedures
	…, after patient eligibility has been confirmed	… after patient eligibility has been confirmed. **Instruct the patient to take Day 1 dose on the day of this visit.**	Clarified procedures
	• Record the visit in IWRS and dispense investigational product ` Instruct the patient to begin dosing on the day. (Second to last bullet) …the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed.	• Record the visit in IWRS and dispense investigational product – Instruct the patient to begin dosing on the day **of the Day 1 visit.** …the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed. **Instruct the patient to take Day 1 dose on the day of this visit.**	Updated procedures to match updated protocol design.

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9.7.6, Week 3 Safety Visit Procedures	Week 3 ~~(~~Safety ~~Contact)~~	Week 3 Safety **Visit Procedures**	Updated procedures to match updated protocol design per PMR requirements.
	~~Patients should be contacted by telephone at Week 3 to assess for AEs and verify that s/he~~ is dosing as directed. • ~~Contact~~ patient ~~by~~ ~~phone/email~~.	**Preferably, the patient will come in to the clinic for this visit. Alternatively, the site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.** **Verify that patient** is dosing as directed. • **Verify that the** patient **has fasted for at least 8 hours.** ` **Record fasting status in the source and eCRF** • **If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.** • **Review and record prior concomitant medications.** • **Assess and record AEs.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess investigational product compliance, perform investigational product accountability**	
		• Obtain blood samples for ` **Serum chemistry, hematology, and coagulation** **Schedule the next visit, reiterate dosing instructions, and advise the patient:** **Week 6 visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 visit within the following Wednesday and Friday (Figure 2).** • ` **NOT to take investigational product on the morning of the next visit, and**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		` **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** ` **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.**	
9.7.8, Week 9 through Week 48 (Safety Contact)	(Insertion)	**Patients should be contacted by telephone/email at Week 9 and every 3 weeks afterward to Week 48.** • **Contact patient by phone/email.** • **Review and record prior concomitant medications.** • **Assess and record AEs.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess investigational product compliance, perform investigational product accountability.**	Section added to provide guidance for telephone/email safety contact.
9.7.9, Week 12, Week 24, Week 36 Procedures	Week 12 Procedures Obtain blood samples ~~for markers of inflammation~~ ` ~~ELF (including HA, P3NP, and TIMP-1)~~ ` C4, ~~and~~ FGF-19, ~~bile acids~~ ` ~~Trough~~ PK assessment	Week 12, **Week 24, Week 36** Procedures • **Assess investigational product compliance, perform investigational product accountability** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible. (Refer to Section 7.3)** • Obtain blood samples for ` **Serum chemistry, hematology, and coagulation** ` **Markers of Inflammation (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30)** ` **Bile Acid**/C4/FGF-19	Updated procedures to match updated protocol design.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		Fasting PK assessment • **Perform a urine-based β-hCG pregnancy test in females of childbearing potential.** • **Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit.**	
	• Serial PK assessment; the following procedures will be conducted in all patients	• Serial PK assessment at **Week 12 and 24 ONLY (not done at Week 36 and Week 42);** the following procedures will be conducted in all patients	Updated procedures to match updated protocol design.
9.7.9, Week 12, Week 24, Week 36 Procedures	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
	Insertion	• Perform an ultrasound for HCC surveillance at **Week 24 ONLY** (if equipment is unavailable, sites should make every attempt to use available community referral sites).	
	• ~~Assess the patient's supply of investigational product to ensure an adequate amount.~~	deleted	Deleted for clarity.
9.7.10 Week 18 and Week 30 Procedures		Added the following procedure: • **Dispense investigational product only if there is dose increase or as needed. No new IP bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each IP bottle before a new bottle will be dispensed.**	Section merged into 9.7.8, additional PK assessments added per

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	— Obtain blood samples ~~for markers of inflammation~~ ~~ELF (including HA, P3NP, and TIMP-1)~~ C4, ~~and~~ FGF-19, ~~bile acids~~ ~~Trough~~ PK assessment Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose	• Obtain blood samples for – **Serum chemistry, hematology, and coagulation** – **Markers of inflammation and fibrosis (IL 6, hs-CRP, TNF α, IgM, IgG, IgA, CK 18 M30, ELF [HA, P3NP, and TIMP 1])** – **Fasting** PK assessment – **Bile Acid**/C4/FGF-19 • Serial PK assessment at **Week 12 and 24 ONLY (not done at Week 36)**; the following procedures will be conducted in all patients: Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 **7, 8, 9, and 24** hours post dose	PMR requirements.
	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume a **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
9.7.10, Week 24 Procedures	~~9.7.10, Week 24 Procedures~~	deleted	Incorporated into Section 9.7.8
9.7.11, Week 48 Procedures	9.7.1~~2~~	9.7.1**0, Week 48 Procedures**	Updated language.
	• Perform a physical examination,	• Perform a physical examination, **including smoking and alcohol consumption history, and current habits for both**	Clarify study procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	(Insertion)	• **Assess investigational product compliance, perform investigational product accountability.** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed**. • **Assess for dose titration, if eligible (refer to Section 7.3)** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	Clarify study procedures.
	Obtain blood samples ~~for markers of inflammation~~ ` ~~ELF (including HA, P3NP, and TIMP-1)~~ ` C4, ~~and~~ FGF-19, ~~bile acids~~ ` ~~Trough~~ PK assessment	• **Perform urinalysis (dipstick)** • Obtain blood samples for – **Serum chemistry, hematology, and coagulation** – **Markers of inflammation and fibrosis (IL 6, hs-CRP, TNF α, IgM, IgG, IgA, CK 18 M30, ELF [HA, P3NP, and TIMP 1])** – **Fasting** PK assessment – **Bile Acid**/C4/FGF-19	Clarify study procedures.
	• Serial PK assessment; will ~~only~~ be conducted in patients ~~who are uptitrating to the next dose level.~~	• Serial PK assessment; **the following procedures** will be conducted in **all** patients.	Updated language.
		Immediately following 1 hr post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes)	Added more sampling times.

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		` Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, **7, 8, 9, and 24** hours post dose.	
	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
	Perform TE using the Fibroscan® TE device.	Perform TE using the Fibroscan® TE device. **If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.),** the **procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit**.	Clarified procedural instructions.
	• ~~Assess the patient's supply of investigational product to ensure an adequate amount.~~		Clarified procedural instructions
	• Schedule the ~~follow up~~ visit and advise the patient:	• Schedule the **next** visit**, reiterate dosing instructions**, and advise the patient: ` **NOT to take investigational product on the morning of the next visit, and** ` **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** ` **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted**.	Clarify study procedures.
9.7.12, Every 3 Months after Week 48	9.7.1~~3~~ Patients who have completed their 48-week double-blind treatment period will continue double blind treatment until all randomized patients have completed their ~~participation in the primary~~ treatment period and the database is locked…. and should not exceed the indicated maximal dose and frequency indicated for their CP category.	**9.7.11. Every 3 Months after Week 48** **<u>Quarterly</u>** • **Verify that the patient has fasted for at least 8 hours.** – **Record fasting status in the source and eCRF** – **If the patient reports having eaten within 8 hours, document accordingly in the source and**	Clarified dispensing instructions.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~Patients will then have the option to continue into an open-label LTSE.~~	**eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.** • **Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess and record vital signs (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Perform assessments for calculation of CP Score (Section 14.1.1).** • **Administer Quality of Life and Patient questionnaires (see Section 13.2.6).** • **Assess investigational product compliance, perform investigational product accountability.** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible (refer to Section 7.3).**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		• **Perform urinalysis (dipstick)** • **Perform a urine-based β-hCG pregnancy test in females of childbearing potential.** • **Obtain blood samples for** – **Serum chemistry, hematology, and coagulation** • **Schedule the next visit, reiterate dosing instructions, and advise the patient:** – **NOT to take investigational product on the morning of the next visit, and** – **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** • **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.** **Patients will complete a TE/ELF (HA, P3NP and TIMP 1) and ultrasound (for HCC surveillance) assessment, every 6 months (±2 weeks) after Week 48.** **ECG will be done yearly (±2 weeks) after Week 48.**	
9.7.13, End of Study/Early Termination Procedures for Patients that Withdraw from Investigational Product or	9.1.14; End of ~~Treatment~~/Early Termination Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent … Patients who discontinue investigational product before are expected to continue … EOT/ET procedures will be required whenever patients discontinue treatment with investigational product	9.7.1**2**. . End of **Study**/Early Termination/**End of Treatment** Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent … Patients who discontinue investigational product **before Week 48** are expected to continue ... EOT (when subject discontinues investigational product)/ET procedures will be required whenever patients discontinue treatment with investigational product (**Table 1, Section 9.7.10**)	Clarified procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Withdraw Consent	When a patient discontinues investigational product ~~but~~ continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. (Insertion)	When a patient discontinues **or interrupts** investigational product **and** continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. **EOT and EOS visits are encouraged but at no time will a missed EOT or EOS visit be considered a protocol deviation.**	
9.7.13, Table 5, row 5	~~Treatment Interruption Interrupted RetainedRegular Visit Schedule Complete as close as possible to last dose of investigational product Complete at final study visit~~	Deleted	Removed to reduce confusion
10.3, Investigational Product Storage	~~Investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15ºC to 25ºC.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical studies are to be shipped and stored at 15˚C to 25˚C. Temperature excursions within the range of 2˚C and 30˚C for no more than a 6-month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20˚C to 40˚C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.**	Updated storage conditions per the Investigator's Brochure.
12, 12.1, Pharmacokinetic Blood Sampling	~~Subjects~~ with at least one PD assessment after dosing will be included in the combined PK/PD analyses Serial and ~~trough~~ PK assessments will be performed in all patients participating in the study. ~~At each visit~~, patients will provide…	**Patients in the PK Population** with at least one PD assessment after dosing will be included in the combined PK/PD analyses Serial and **fasting** PK assessments will be performed in all patients participating in the study. **At Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48**, patients will provide…	Specific dates are required to obtain optimum PK results

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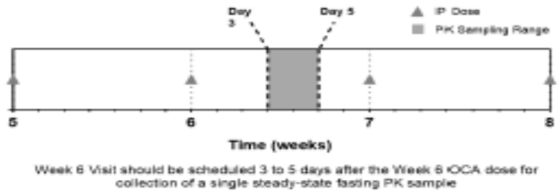
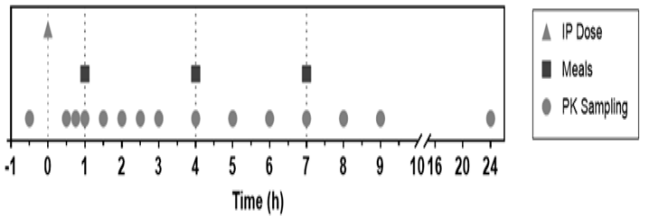
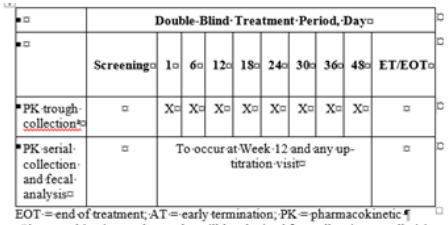
	(Insertion)	**Week 6 visit should occur 3, 4, or 5 days after the Week 6 dose, (eg if the Week 6 dose of drug is taken on a Sunday, the patient should come in for the Week 6 visit between Wednesday and Friday [Figure 2]).**	
	(Insertion) …serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose…	**Figure 2: Week 6 Sampling Schedule**  Week 6 Visit should be scheduled 3 to 5 days after the Week 6 OCA dose for collection of a single steady-state fasting PK sample **IP = investigational product; PK = pharmacokinetic** **At Weeks 12, 18, 24, 30, and 48,** Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5**,** 6, **7, 8, 9 and 24 hours postdose (Figure 3) for all patients. The patient will be given the option to return** to the **clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. The home health care agency must be advised one week in advance of the appointment.**	Added diagram and language to clarify PK sampling procedures.
	(Insertion)	**Figure 3: Pharmacokinetic Sampling Schedule**  At meal timepoints, meals are consumed immediately after the collection of the PK sample **OCA = obeticholic acid; PK = pharmacokinetic**	Added diagram and language to clarify PK sampling procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
12.1, Pharmacokinetic Blood Sampling	~~Table 7: Pharmacokinetic Sampling Schedule~~  Double Blind Treatment Period, Day Screening | 1 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | ET/EOT PK trough collection[a] | X | X | X | X | X | X | X | X PK serial collection and fecal analysis | To occur at Week 12 and any up-titration visit EOT = end of treatment; AT = early termination; PK = pharmacokinetic [a] Pharmacokinetic trough samples will be obtained from all patients at all visits prior to dose administration. [b] Serial PK assessments will be performed in all patients at Week 12. Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible and uptitrated their dose. Sample collection for fecal analysis will occur concurrent serial PK sampling visits only.		Replaced with other Figures 2 and 3.
	During the ~~double blind~~ treatment period and ~~double blind LTSE:~~ • Pharmacokinetic ~~trough~~ samples will be obtained from all patients at all visits prior to dose administration in accordance with ~~Table 7~~. • Serial PK assessments will be performed in all patients ~~at Week 12~~. ~~Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible~~ and ~~uptitrated their dose~~. ~~Sample collection for fecal analysis will occur concurrent with serial PK sampling visits only.~~	During the treatment period: • Pharmacokinetic **fasting** samples will be obtained from all patients at **Weeks 6, 12, 18, 24, 30, 36, and 48** prior to dose administration in accordance with **Figure 3**. • Serial PK assessments will be performed in all patients **at Weeks 12, 18, 24, 30, and 48.**	Clarify PK sampling and collection procedures.
12.2, Processing and Handling of Pharmacokinetic Samples	The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site and in a separate document before the study is initiated.	The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site **and home health care company** in a separate document before the study is initiated.	Added option of using home health care service.
13, Assessment of Safety	~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.~~ ~~Safety will be assessed in terms of AEs. All AEs, whether observed by the investigator, reported by the patient, noted from laboratory findings, or identified by other means, will be recorded from the time the patient signs his/her consent~~	deleted	Safety information updated to match Protocol 747-302.

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td></td><td>~~form (s)until the patient completes study participation (final Follow Up Visit).~~
~~Recording AEs/SAEs in the electronic data capture (EDC) system is the method for reporting AEs/SAEs. It is therefore imperative, that AEs/SAEs are recorded into the EDC.~~</td><td></td><td></td></tr>
<tr><td rowspan="2">13.1.1.3. Treatment-Emergent Adverse Event</td><td>13.1.1.~~2~~
~~A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.~~</td><td>Moved to Section 13.1.3. Recording Adverse Event Severity</td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>~~Table 9: Severity of Adverse Events~~
<table><tr><th>Grade</th><th>Clinical Description of Severity</th></tr><tr><td>~~1=Mild~~</td><td>~~Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.~~</td></tr><tr><td>~~2=Moderate~~</td><td>~~Minimal, local or noninvasive intervention indicated, or limiting age-appropriate instrumental activities of daily living.~~</td></tr><tr><td>~~3=Severe~~</td><td>~~Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.~~</td></tr></table></td><td>Table 9: Severity of Adverse Events
<table><tr><th>Grade</th><th>Clinical Description of Severity</th></tr><tr><td>1=Mild</td><td>Causing no limitation of usual activities; the patient may experience slight discomfort.</td></tr><tr><td>2=Moderate</td><td>Causing some limitation of usual activities; the patient may experience annoying discomfort.</td></tr><tr><td>3=Severe</td><td>Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.</td></tr></table></td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.3.1. Severity of Pruritus (as an Adverse Event)</td><td>~~To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used for AE reporting. As pruritus is a patientive symptom, clinical judgment should be used to determine its severity and management Table 10~~
Table 10 deleted.</td><td></td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.4.1. Reporting of Adverse Events</td><td>(Insertion)</td><td>…. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.</td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.4.2. Reporting of</td><td>• ~~Telephone:~~ PPD
If an SAE is reported by ~~telephone or~~ fax, …</td><td>If an SAE is reported by fax, …</td><td>Number no longer in use.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Serious Adverse Events			
13.1.5.1. Potential Clinical Outcome Events	~~The events listed below will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events. These events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.~~ ~~Potential Clinical Outcome Events:~~ ~~Hospitalization for clinical complications of cirrhosis.~~ ~~Given that the Potential Clinical Outcome Events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously report suspected Potential Clinical Outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a "potential study event" on the Adverse Event eCRF and will be submitted for adjudication to the Adjudication Committee as described in Section 15.9.~~		Safety information updated to match Protocol 747-302.
13.1.7. Notification of Post-Treatment SAEs for Patients Who Continue in the Study	13.1.7. Notification of Post-~~Study~~ SAEs ~~If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2~~	13.1.7. Notification of Post-**Treatment** SAEs **for Patients Who Continue in the Study** **Post-treatment SAEs that occur in patients who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.** **SAEs that occur in patients who discontinue investigational product, initiate treatment with commercially available Ocaliva, and remain in the study must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2**.	Safety information updated to match Protocol 747-302. Deleted text is already in Section 13.1.8.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
13.1.8. Notification of Post--Study SAEs	(Insertion)	**13.1.8. Notification of Post-Study SAEs** **All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.**	Safety information updated to match Protocol 747-302.
13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	~~13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study~~ ~~Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2~~	Moved to 13.1.7	Safety information updated to match Protocol 747-302 9 (moved to 13.1.7).
13.1.10, Pregnancy and Follow-up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must ~~discontinue~~ investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing. ~~In the situation that the EDC is not functioning, the Medical Monitor should be notified by telephone. The investigator remains responsible for entering the pregnancy information into the EDC when the EDC becomes functional.~~	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must **interrupt treatment with** investigational product immediately (see Section) and the Sponsor must be notified within 24 hours of the Investigator's **awareness** of the pregnancy by completing the Pregnancy **CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to** PPD **or faxed to** PPD **The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.** **The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The patient must have a negative pregnancy test before restarting investigational product. If a patient's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy**	Safety information updated to match Protocol 747-302.

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		confirmed by a serum β-hCG test before restarting investigational product.	
13.2.2, Physical Examination	13.2.~~1~~ (Insertion)	13.2.**2** A basic physical examination… **Smoking and alcohol consumption history and current habits will be recorded**….	Clarified assessments
13.2.5, Laboratory Assessments	~~For visits that require fasting~~, the Investigator or designee will verify that the patient has fasted for at least 8 hours …	**At all visits (except screening),** the Investigator or designee will verify that the patient has fasted for at least 8 hours…	Clarified visit procedures
	Blood samples for serum chemistry, coagulation, and hematology will be collected at ~~every visit~~…	Blood samples for serum chemistry, coagulation, and hematology and **urine samples** will be collected at **visits**…	Clarified what samples will be collected.
13.2.5, Laboratory Assessments, Table 9		Added the following labs: • Serum Chemistry – **CPK, TFT (TSH, free T3 and free T4)** • Urinalysis **(dipstick)** – **Pregnancy** • Noninvasive measurement… – **ELF (HA, P3NP, and TIMP-1), TE**	Updated lab tests to be performed.
	~~Biomarkers~~ of ~~Hepatic Fibrosis and/or~~ Inflammation; IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30, ~~and others as determined during course of study~~	Markers of Inflammation; IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30	Clarified assessments
	~~Genetics; DNA including single nucleotide polymorphisms that may be involved in PBC; RNA~~	deleted	No longer doing this analysis.
13.2.5, Laboratory Assessments	(Insertion)	**PD markers**: C4, **FGF-19 and plasma bile acids**	Added new row

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td>13.2.5, Laboratory Assessments</td><td>(Insertion)</td><td>Laboratory reference ranges for the study will be based on the laboratory vendor range.</td><td>Added to satisfy PMR request.</td></tr>
<tr><td>14.1.1, Child-Pugh Score, Table 10</td><td><table>
<tr><th>Factor</th><th>Units</th><th>Points</th><th></th><th></th></tr>
<tr><th></th><th></th><th>1</th><th>2</th><th>3</th></tr>
<tr><td><s>Serum bilirubin</s></td><td><s>µmol/L</s></td><td><s><35</s></td><td><s>35-50</s></td><td><s>>50</s></td></tr>
<tr><td><s>Serum albumin</s></td><td><s>g/L</s></td><td><s>>35</s></td><td><s>28-35</s></td><td><s><28</s></td></tr>
<tr><td>Hepatic encephalopathy</td><td></td><td><s>No</s></td><td></td><td></td></tr>
</table></td><td>Deletion

Encephalopathy now 0</td><td>Simplified CP scoring procedure.</td></tr>
<tr><td>14.2.1, Markers of Inflammation, Apoptosis and Necrosis</td><td>Blood samples for analytes including hs-CRP, IgM, TNF-α, and cytokeratin-18, neoepitope M30.</td><td>Blood samples for analytes including IL-6, hs-CRP, IgA, IgG, IgM, TNF-α, and cytokeratin-18, neoepitope M30.</td><td>Added additional markers.</td></tr>
<tr><td>15.4, Safety Analyses</td><td>No inferential comparison <s>of safety endpoints</s> will be performed. <s>All</s> safety <s>comparisons will be descriptive.</s></td><td>No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.</td><td>Clarified statistical analyses.</td></tr>
<tr><td>15.4.3, Adverse Events of Special Interest</td><td>… The <s>quartiles, including</s> the median <s>time-to-event</s> and <s>their respective</s> 2-sided 95% CIs, will be presented. <s>KM estimates will be plotted</s> as <s>a “survival curve” for each treatment group.</s></td><td>… The tabulation will include the KM estimate methodology using 25th, 50th (median), and 75th percentiles of the medians and corresponding with associated 2-sided 95% confidence intervals (CIs), if the medians can be estimated as well as percentage of censored observations.</td><td>Clarified statistical analyses.</td></tr>
<tr><td>15.5, Efficacy Analyses, 4th paragraph</td><td>… The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 95% CI of the difference will also be presented. <s>No formal hypothesis testing will be performed.</s></td><td>The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 2-sided 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 2-sided 95% CI of the difference will also be presented</td><td>Clarified statistical analyses.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
15.6, Additional Efficacy Analyses	The following clinical ~~outcomes~~ will be captured in the study: • All cause ~~mortality~~ • Liver related death • Liver transplant • Variceal bleed • Hepatic encephalopathy • Bacterial peritonitis • ~~Ascites~~ • ~~Hepatocellular carcinoma~~	The following clinical **endpoints** will be captured in the study : • **Time to death** (all-cause) • **Time to** liver-related death • **Time to hepatic failure** leading to liver transplant • **Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)** • **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:** – **Time to variceal bleed** – **Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)** – **Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)** • **Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).** The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-	Clarified statistical endpoints.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata. **In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC) will be summarized by treatment group using the same methods as defined above.**	
18.3, Written Informed Consent	(Insertion)	**The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the patient.**	Updated language.
21, List of References	(Insertion)	**Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014 Sep;61(3):642-59**. **Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007 Mar;45(3):797-805.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-72.**	Added new references
Appendix A, List of Study 747-401 Outcome Events	~~Some of the specified clinical endpoints will also by definition (see Section 13.1) qualify as Serious Adverse Events (SAEs). The sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 13.1.4). The Sponsor is responsible for regulatory reporting of SAEs including expeditious reporting of SAEs that are considered related to the investigational product and considered Unexpected by regulatory standards as defined in the Investigational Brochure.~~		This is covered in the main text.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~The Sponsor may consider the following lists of events to be exempt from expeditious regulatory reporting but will continue to report them in a non-expeditious manner:~~ ~~Potential Clinical Outcome Events:~~ ~~Liver-related events resulting in death~~ ~~Hepatic failure leading to liver transplant~~ ~~Variceal bleed~~ ~~Hepatic encephalopathy~~ ~~Spontaneous bacterial peritonitis~~ ~~Ascites~~ ~~Hepatocellular carcinoma~~		

Clinical Study Protocol 747-401

OBETICHOLIC ACID (OCA)

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

Version 3: 04 Jan 2018

EudraCT Number: 2017-001762-13

Sponsor

Intercept Pharmaceuticals, Inc.
4760 Eastgate Mall
San Diego, CA 92121
USA

TEL: +1 858 652 6800

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD , PhD

09 Jan 2018
Date

Sr Vice President, Clinical Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-401. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected patients according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-401 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human patients in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

Medical Monitor

Primary Contact:	PPD MD Senior Medical Director, Clinical Division INC Research/inVentiv Health PPD PPD
Secondary Contact:	PPD DO, MSPH Senior Medical Director Intercept Pharmaceuticals, Inc. (Intercept) PPD
24-Hour Telephone:	PPD
SAE Fax:	PPD
SAE Email:	PPD

2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; (6-ECDCA)

Title of Study:

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

Investigators and/or Study Center(s):

The study is planned to have approximately 35 investigational sites, globally.

Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.	**Phase of Development:** Phase 4: US, Canada, and the EU Phase 3b: All other regions

Objectives:

Primary Objective:

- To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

Secondary Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - The model of end stage liver disease (MELD) score and its components
  - Child-Pugh (CP) score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

Additional Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD parameters and safety and tolerability assessments
- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ])

- To assess clinical events consistent with end-stage liver disease
  - Death (all-cause)
  - Liver transplant
  - MELD score ≥15 (for patients with MELD ≤12 at baseline)
  - 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
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

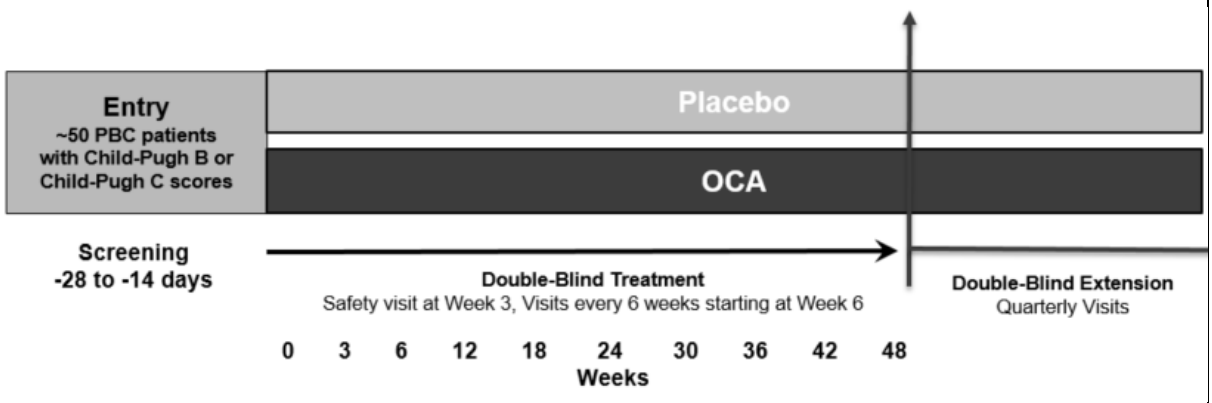
Methodology: This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with primary biliary cholangitis (PBC) and moderate to severe hepatic impairment defined as Child-Pugh B (CP-B) (moderate) and Child-Pugh C (CP-C) (severe) including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. Titration may be considered as early as the Week 12 Visit. Fasting PK assessments will be performed in all patients participating in the study on Day 1, Week 6, and Week 36. Serial PK sampling (which also includes a fasted PK assessment) will be performed at Week 12, 18, 24, 30, and 48.

Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

Study Design Diagram



OCA = obeticholic acid, PBC = primary biliary cholangitis

Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.

Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

Dosing Regimen:

All patients will initiate investigational product once weekly with 5 mg OCA or matching placebo. Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.

Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

Planned OCA or Matching Placebo Dosing Regimen

	Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)	
	Treatment Group	
	OCA	Placebo
Starting Dose (Day 1)	5 mg once weekly	matching placebo once weekly
Titration 1[a]	5 mg twice weekly[b]	matching placebo twice weekly[b]
Titration 2[a]	10 mg twice weekly[b]	matching placebo twice weekly[b]

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Number of Patients (planned): Approximately 50 patients will be enrolled in this study.

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines, defined as having ≥2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
    - Liver biopsy consistent with PBC (collected at any time prior to Screening)
2. Evidence of cirrhosis including at least one of the following:
    - Biopsy results consistent with PBC Stage 4
    - Liver stiffness as assessed by TE Value ≥16.9kPa
    - Clinical evidence in the absence of acute liver failure consistent with cirrhosis including: gastroesophageal varices, ascites, radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
    - Combined low platelet count (<140 000/mm^3) with
        - persistent decrease in serum albumin, or
        - elevation in prothrombin time/INR (not due to antithrombotic agent use), or
        - elevated bilirubin (2× ULN)
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening:
    - Moderate: CP-B (Scores 7 to 9) or
    - Severe: CP-C (Scores 10 to12)
4. MELD score of 6 to 24 at Screening
5. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate or unresponsive to UDCA (no UDCA for ≥3 months)

Key Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. Current hepatic encephalopathy (as defined by a West Haven score of ≥2)
5. History or presence of other concomitant liver diseases including:
    - Hepatitis C virus infection and RNA positive
    - Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the Medical Monitor
    - Primary sclerosing cholangitis
    - Alcoholic liver disease
    - Definite autoimmune liver disease or overlap hepatitis
    - Gilbert's Syndrome

6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function prior to randomization

Investigational Product, Dosage and Mode of Administration:

OCA 5 mg or OCA 10 mg tablets, oral administration

Placebo tablets, matched in size and appearance to OCA tablets, oral administration

Duration of Treatment:

Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

Criteria for Evaluation:

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus, and fatigue
Secondary Objectives	**Assessments**
Changes in risk scores	Changes in MELD and in CP scores and components of the CP score and MELD score
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma bile acids
Additional Objectives	**Assessments**
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	TE and ELF (HA, P3NP, and TIMP-1)
PK/PD relationship	PK parameters compared to PD parameters and safety and tolerability assessments (above)
Patient-reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
Clinical events	Death (all-cause and liver-related), liver transplant, MELD score ≥15 (for patients with MELD ≤12 at baseline), hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and HCC.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; INR = international normalized ratio; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PBC = Primary Biliary Cholangitis; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TE = Transient Elastography; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; VAS = visual analog scale

Statistical Methods:

Analysis Populations:

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK Population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

Pharmacokinetic Analyses:

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, metabolite OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.

Safety Analyses:

Safety analyses will be conducted using the Safety population. Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group. The incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs) will be tabulated by system organ class and preferred term for each treatment group, and similarly by severity and relationship to treatment. Laboratory parameters, physical examinations including vital signs, and electrocardiograms will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.

Efficacy Analyses:

This study does not plan to conduct a formal hypothesis testing for any efficacy endpoint.

The endpoints of efficacy assessments are change in total and direct bilirubin, INR, creatinine, albumin, platelets, ALP, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline values as covariates. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Additional Efficacy Analyses

Analyses of changes in liver stiffness (TE) and liver fibrosis (ELF [HA, P3NP, and TIMP-1]) will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.

The following endpoints consistent with end-stage liver disease will be captured in the study:

- Time to death (all cause)
- Time to liver-related death
- Time to liver transplant
- MELD score ≥15 (for patients with MELD ≤12 at baseline)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Time to variceal bleed

- Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)
- Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)

- Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

The incidence and time to first occurrence of any of the above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of HCC will be summarized by treatment group using the same methods as defined above.

Sample Size Justification:

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. A total of 30 patients is adequate with 10 patients on placebo to be included as a comparator and 20 patients on OCA. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Placebo and OCA.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
6-ECDCA	6α-ethyl chenodeoxycholic acid (also known as INT-747)
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
BP	blood pressure
C4	7α-hydroxy-4-cholesten-3-one
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CRA	Clinical Research Associate
CP	Child-Pugh
eCRF	electronic case report form
DDI	drug-drug interaction
DMC	Data Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation or Specialist Term	Explanation
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid
HCC	hepatocellular carcinoma
HCP	health care professional
HDL	high-density lipoprotein
IB	Investigational Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
ITT	intent-to-treat
IWRS	interactive web response system
KM	Kaplan-Meier
LDL	low-density lipoprotein
LTSE	long-term safety extension
LS	least squares
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model of end stage liver disease
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SD	standard deviation
SEM	standard error of the mean
SI	standard international system of units
SOC	system organ class

Abbreviation or Specialist Term	Explanation
StdErr	standard error
SUSAR	suspected unexpected serious adverse reaction
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
the Sponsor	Intercept Pharmaceuticals, Inc.
TIPS	transjugular intrahepatic portosystemic shunt
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States (of America)
VAS	visual analogue scale
VLDL	very low-density lipoprotein

5. INTRODUCTION

5.1. Overview of Disease State and OCA

Primary biliary cholangitis (PBC, also known as primary biliary cirrhosis [Beuers 2015a, Beuers 2015b, Beuers 2015c]) is a serious, life-threatening, cholestatic liver disease of unknown etiology that, without treatment, frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and necessitates liver transplantation or results in death. PBC is a rare disease with reported prevalence in the US of 40.2/100 000 (Kim 2000). PBC disproportionately affects women approximately 10:1 and is typically diagnosed in patients between 40 to 70 years of age.

Historically, the only approved drug therapy for PBC has been the bile acid, ursodeoxycholic acid (UDCA), a physiological constituent of human bile (Lindor 2009). While UDCA therapy had a marked effect on the treatment of PBC, up to 50% of patients showed a suboptimal response or no response to UDCA. Such patients were at significantly increased risk of a poor clinical outcome due to PBC disease progression.

Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist and modified bile acid derived from the primary human bile acid chenodeoxycholic acid (CDCA) (Pellicciari 2002), was developed for the treatment of PBC and to provide patients who have an inadequate response to or poor tolerance of UDCA a novel treatment option that was safe and effective.

In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication, and in May 2017 Ocaliva received approval from Health Canada. Study 747-401 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC (ie, in the US, Canada, and the EU). In all other regions, this study is considered Phase 3b.

5.2. Nonclinical Experience with Obeticholic Acid

Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.

5.3. Clinical Development of Obeticholic Acid

As of 13 Oct 2017, approximately 2690 subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 552 patients had PBC, 1141 patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, 73 patients had primary sclerosing cholangitis (PSC), and 6 patients had biliary atresia.

Overall, the pharmacokinetic (PK) profile of OCA is consistent with that expected of a bile acid. Phase 1 studies demonstrated that OCA is rapidly absorbed and extensively conjugated with

glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates are primarily eliminated via biliary excretion, and plasma concentration time profiles demonstrated multiple peaking with prolonged exposure, indicative of enterohepatic circulation. Plasma concentrations of OCA and its conjugates spike shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.

The OCA clinical development PBC program was based on a wide range of studies in PBC patients and healthy volunteers. The clinical pharmacology studies supported the proposed dosing regimen: 10 mg fixed dose and a titration regimen starting at OCA 5 mg with titration to 10 mg based on clinical and biochemical response. The clinical program included a pivotal Phase 3 clinical study (747-301) and two Phase 2 clinical studies (747-201 and 747-202), which formed the primary basis of approval of OCA.

Study 747-201 (59 patients) evaluated 2 doses of OCA (10 mg and 50 mg) given as monotherapy versus placebo. Statistically significant and clinically relevant relative and absolute reductions from Baseline in alkaline phosphatase (ALP) were achieved with both doses of OCA versus placebo ($p < 0.0001$). Mean relative ALP reductions were 45% (OCA 10 mg) and 38% (OCA 50 mg) compared to an increase of 0.4% with placebo. Further, significant improvements in gamma-glutamyl transferase (GGT) and in conjugated bilirubin were observed with both doses compared with placebo ($p < 0.05$). OCA also resulted in decreased circulating alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Study 747-202 (165 patients) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in patients on a stable therapeutic dose of UDCA. Overall, the data from 747-202 were consistent with Study 747-201. Statistically significant and clinically meaningful relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p < 0.0001$). Mean ALP reductions from baseline ranged from 21% to 25% compared to 3% with placebo. Improvements were also seen in GGT and ALT levels and in conjugated bilirubin levels.

Study 747-301 (216 patients) was a Phase 3, double-blind, placebo-controlled, parallel-group study followed by a long-term safety extension (LTSE) using OCA in patients with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of patients reaching specific criteria for ALP and bilirubin (ALP <1.67x upper limit of normal [ULN] with a ≥15% reduction and bilirubin ≤ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to <1.67x ULN with a ≥15% reduction from baseline and a normal bilirubin level after 12 months of therapy. The placebo group experienced a least squares (LS) mean decrease in ALP from baseline of 5%, compared to a significant LS mean decrease of 39% in the OCA 10 mg dose group and 33% in the OCA titration group (both OCA dose groups $p < 0.0001$ versus placebo).

The LTSE phases of both Phase 2 studies and the pivotal Phase 3 study support the long-term safety of OCA and demonstrate a durable therapeutic response.

Study 747-302 is an ongoing randomized, double-blind, placebo-controlled clinical outcomes study, designed to confirm the clinical benefit of OCA treatment in patients with PBC. This study is inclusive of patients with early to advanced stage PBC.

5.4. Rationale for Study Design and Dose for Investigational Product

5.4.1. Rationale for Study Design

There are limited clinical data available to support the use of OCA in patients with PBC with moderate to severe hepatic impairment. The current recommended dosing of such patients is based on modeled systemic and hepatic concentrations. Therefore, Study 747-401 is specifically designed to characterize the PK, safety, and efficacy of OCA in this patient population.

PK and safety parameters will be evaluated as the primary objectives and efficacy parameters will be evaluated as secondary and additional objectives. While the prognostic utility of ALP has been established by the Global PBC study group, increasing levels of bilirubin are more relevant to understanding the progression of end stage liver disease. Consistently, bilirubin is a key marker of advancing disease as characterized by the Global PBC study group as well as its incorporation into model of end stage liver disease (MELD), Child-Pugh (CP), and Mayo risk scores. As such, the potential of OCA to stabilize bilirubin levels will be evaluated.

In order to generate data for the patient population in a timely fashion, Study 747-401 is designed with a relatively short-term, 1-year double-blind treatment period to gather primarily PK and safety data. Therefore, the study will not formally test the long-term efficacy of OCA on clinical outcomes.

Although Study 747-401 is not designed to formally evaluate clinical outcomes, these data will be collected and assessed as an additional objective. Given the importance of evaluating clinical outcomes in patients with the most advanced form of the disease, these events will be prospectively adjudicated consistent with the procedures implemented in ongoing PBC studies. This will allow for a more robust meta-evaluation of clinical outcomes in patients with moderate to severe hepatic impairment following the completion of both studies.

Study 747-302 is specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment. Data collected from Study 747-401 will serve as a bridge to the 747-302 study.

Taken together, data from this study will complement the data from Study 747-302 and offer the opportunity to better inform the benefit risk profile and appropriate treatment of hepatically-impaired patients.

5.4.2. Rationale for Obeticholic Acid Dose and Duration

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (CP Score). Model simulations predicted that for mild (Child-Pugh A [CP-A]), moderate (Child-Pugh B [CP-B]), and severe (Child-Pugh C [CP-C]) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to patients with normal hepatic function, whereas total OCA liver concentrations increase 1.1-, 1.5-, and 1.7-fold, respectively. Because the liver is the primary site of action for the safety and efficacy of OCA, it is important to account for the differences in systemic and liver exposure when assessing effective doses. It is also important to note that while hepatically impaired (CP-B and C) patients treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy patients, no apparent impact on the overall safety profile was observed, consistent with only a modest

increase in liver exposure of OCA associated with hepatic impairment. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).

5.4.3. Rationale for Population Chosen

Patients with PBC and moderate or severe hepatic impairment, based on CP score and varying levels of MELD, are the targeted population for this study as OCA has been studied primarily in early to moderate stages of liver impairment in patients with PBC. There is a great need to extend therapies to PBC patients with more advanced liver impairment. Given the unmet medical need and observed efficacy, safety and tolerability profile of OCA in early and moderate PBC, evaluating the effects of OCA in a late stage population is warranted.

5.4.4. Rationale for Control Group

The use of a randomized placebo control group added to established standard of care provides the best scientific evidence of efficacy and safety. The use of a placebo control provides a concurrent comparator group, accounting for not only a placebo effect but continued standard of care. The use of a placebo control is critical to assess the safety and tolerability of OCA but also as a comparator for the high rate of clinical events which are expected in this advanced population.

5.5. Importance of Monitoring of Disease Progression

Given PBC is a chronic, progressive liver disease, it is important that patients with PBC are closely monitored to ensure early identification of decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve patient oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual patients to determine on an ongoing basis the totality of a patient's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring.

Patients will be monitored for potential hepatic injury and/or decompensation. Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 8.4 and Section 7.6. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.

5.6. Summary of Known Potential Risks with Investigational Product

The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk.

Clinical Data

In two Phase 2 studies and a Phase 3 study evaluating OCA in the treatment of subjects with PBC, hepatic adverse events were observed in subjects receiving doses of OCA ranging from the maximum approved dose of 10 mg once daily to 50 mg (5 times the highest recommended dose).

Recent safety findings in NASH clinical trials include 2 cases of hepatic decompensation reported as SUSARs, 1 of which resulted in death. Both cases involved numerous confounding factors that make evaluation of association with treatment difficult. Details for both events are provided in the Investigator's Brochure Addendum 1 to Version Number: 16 (31 March 2017), Effective Date: 02 October 2017.

The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease.

Changes in lipid profiles have also been observed with OCA dosing, including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further.

Independent data monitoring committees (DMCs) have performed detailed reviews of several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification.

Post-Marketing Cases in PBC

As of September 2017, greater than 3000 patients have received Ocaliva® in the post-marketing setting. In patients with moderate to severe hepatic impairment (Child-Pugh B and C), liver decompensation, liver failure, and death have been reported when Ocaliva was dosed up to 7 times the recommended once weekly starting dose for such patients. Based on the initial medical assessment of these cases, which included patients having undergone liver transplant, there was insufficient evidence suggesting a causal relationship between higher than recommended dosing and the reported adverse events. However, Intercept Pharmaceuticals, Inc. (the Sponsor) continues to assess the potential association between adverse events, including deaths, and the higher than recommended dosing of Ocaliva observed in PBC patients with moderate to severe hepatic impairment (Child-Pugh B and C) through ongoing post-marketing pharmacovigilance activities.

Signs and symptoms reported in patients experiencing liver-related adverse events who received Ocaliva include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new

or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice, and liver decompensation.

Refer to the IB for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

The study will be conducted in patients with PBC and moderate to severe hepatic impairment defined as CP-B and CP-C with MELD scores ranging from 6 to 24.

6.1. Primary Objectives

- To evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and OCA metabolite glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

6.2. Secondary Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - The MELD score and its components
  - CP score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

6.3. Additional Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD parameters and safety and tolerability assessments
- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ]

- To assess clinical events consistent with end-stage liver disease
  - Death (all cause)
  - Liver transplant
  - MELD score ≥15 (for patients with MELD ≤12 at baseline)
  - 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
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with PBC and moderate to severe hepatic impairment defined as CP-B and CP-C including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

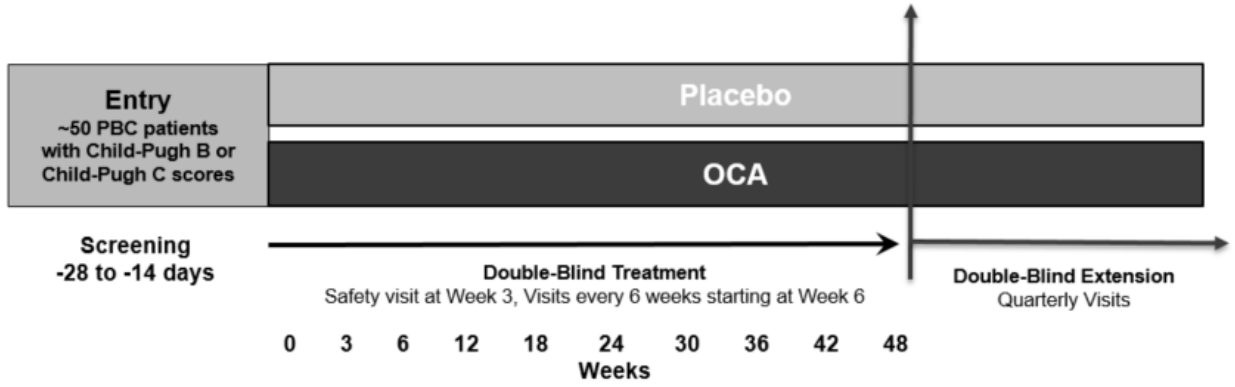
Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Treatment Period: During the 48-week treatment period, an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. Titration may be considered as early as the Week 12 Visit (see Section 7.3). Fasting PK assessments will be performed in all patients participating in the study on Day 1, Week 6, and Week 36. Serial PK sampling (which also includes a fasted PK assessment) will be performed at Week 12, 18, 24, 30, and 48.

Patients who have completed their 48-week, double-blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

7.1.1. Study Design Diagram

Figure 1: Study Design



OCA = obeticholic acid, PBC = primary biliary cholangitis

Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.

Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

			Double-Blind Treatment Period (Weeks)[b]									Double-Blind Extension
	Screening	**Day 1[a]**	**3[c]**	**6[d]**	**12**	**18**	**24**	**30**	**36**	**42[c]**	**48/ ET/ EOS/EOT**	**Every 3 months**
Visit Window (+/-)	**-28 to -14 days**		**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±2 wks**
Fast ≥8 h Prior to Visit[e]	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X											
Medical/PBC History	X											
Inclusion/Exclusion Criteria	X	X										
Physical Exam[f]	X	X		X	X	X	X	X	X		X	X
Vital Signs and Weight	X	X		X	X	X	X	X	X		X	X
Medical and Surgical Procedures		X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Assessments for Child-Pugh Score[g]	X	X		X	X	X	X	X	X		X	X
Patient Questionnaires (Pruritus VAS, PBC-40, EQ- 5D-5L, and CLDQ)[h]		X		X	X	X	X	X	X		X	X
Randomization/Treatment Assigned		X										
Dispense IP[i]		X			X	X	X	X	X	X	X	X
Dose Titration Assessment[j]					X	X	X	X	X	X	X	X
IP Accountability/ Compliance			X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Study Procedures (Continued)

			Double-Blind Treatment Period (Weeks)[b]									Double-Blind Extension
	Screening	**Day 1[a]**	**3[c]**	**6[d]**	**12**	**18**	**24**	**30**	**36**	**42[c]**	**48/ ET/ EOS/EOT**	**Every 3 months**
Visit Window (+/-)	**-28 to -14 days**		**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±2 wks**
Urinalysis	X	X									X	X[p]
Urine-based β-hCG Pregnancy Test[k]	X	X		X	X	X	X	X	X		X	X
Virology (HCV/HBsAg)	X											
Serum Chemistry/Hematology/ Coagulation[l]	X	X	X	X	X	X	X	X	X	X	X	X
Amylase and Lipase	Sample to be collected if the patient experiences acute pancreatitis or cholecystitis.											
PK Fasting Collection		X		X					X			
PK Serial Collection[m]					X	X	X	X			X	
PD Markers: Bile Acid/C4/FGF-19		X		X	X	X	X	X	X		X	
TE/ELF (HA, P3NP, and TIMP-1)[n]		X			X		X		X		X	X[o]
12-Lead Electrocardiogram	X										X	X[p]
Hepatic Ultrasound[q]	X[r]	X[s]					X				X	X[o]
Gallbladder assessment (ultrasound)	X[r]	X[s]										

AE = adverse event; eCRF = electronic case report form; C4 = 7α hydroxy-4-cholesten-3-one; CLDQ = Chronic Liver Disease Questionnaire; ELF = enhanced liver fibrosis; ET = Early Termination; EOS = End of study; EOT = End of Treatment; ; FGF-19 = fibroblast growth factor-19; HA = hyaluronic acid; HCV = Hepatitis C virus; IP = Investigational Product; P3NP = procollagen 3 N-terminal peptide; PBC = primary biliary cirrhosis; PK = pharmacokinetics; TE = transient elastography; wk(s) = week(s), TIMP-1 = tissue inhibitor of metalloproteinase ; VAS = Visual Analogue Scale.

[a] Visit schedule should be based on Day 1. Day 1 visit must occur at least 2 weeks after screening visit.

[b] Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 9 and continuing to Week 48 to assess for AEs, concomitant medications, medical/surgical procedures, and verify that s/he is dosing as directed. (see Section 9.7.8).

[c] Preferably, the patient comes in to the clinic for this visit. Alternatively, site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.

[d] Visit should occur 3, 4, or 5 days after taking the Week 6 dose.

[e] The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, including screening, but water is permitted.
[f] Height and assessment of smoking and alcohol consumption history and current habits will be assessed at Screening and Week 48. Assessment of smoking and alcohol consumption history and current habits will be assessed quarterly after Week 48.
[g] Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF.
[h] The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease.
[i] New investigational product bottles will be dispensed if the patient is up-titrated. Unless up-titrated, patients are expected to use up each investigational product bottle before a new bottle will be dispensed. No new bottles will be dispensed if dose frequency is changed. Patients will be instructed to begin dosing on Day 1, after completing all study assessments. Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.
[j] Dose titration of investigational product may occur starting after the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.
[k] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit (except Week 3). If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally).
[l] MELD values will be calculated based on serum chemistry and coagulation values at each visit.
[m] The patient will be given the option to return to the clinic the following morning for the 24-hour postdose PK sample or samples can be obtained by a home health care designee. Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling.
[n] The noninvasive radiological liver fibrosis measurement devices (such as, FibroScan® device [Echosens; Paris, France]) will be used at all study sites to collect hepatic stiffness measurements.
[o] Patients will complete a TE/ELF and ultrasound assessment, every 6 months (±2 weeks) after Week 48.
[p] ECG and urinalysis will be done yearly (±2 weeks) after Week 48 Visit.
[q] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 1) ultrasounds: Unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm suspected HCC.
[r] If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required.
[s] If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.

7.1.3. Study Duration

Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week, double-blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

7.2. Number of Patients

Approximately 50 patients will be enrolled in this study.

7.3. Planned Dosing Regimen

All patients will initiate investigational product once weekly with OCA 5 mg or matching placebo (Table 2). Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below (Table 2). At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.

Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

Table 2: Planned OCA or Matching Placebo Dosing Regimen

	Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)	
	Treatment Group	
	OCA	**Placebo**
Starting Dose (Day 1)	5 mg once weekly	matching placebo once weekly
Titration 1[a]	5 mg twice weekly[b]	matching placebo twice weekly[b]
Titration 2[a]	10 mg twice weekly[b]	matching placebo twice weekly[b]

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

7.4. Monitoring and Management of Potential Hepatic Injury and/or Disease Progression

Given the chronic nature of PBC, it is important to monitor for potential hepatic injury, disease progression and/or hepatic decompensation. Child-Pugh and MELD scores will be reviewed at each visit where labs are drawn (Table 1). In addition, adverse events, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.2. Based on biochemical and clinical assessments, the investigational product may be interrupted or discontinued per criteria discussed in

Section 7.4.2 and Section 7.4.3, and close monitoring procedures will be implemented (refer to Section 7.6).

7.4.1. Signs and Symptoms of Potential Hepatic Injury or Decompensation

Patients should be instructed to contact study personnel if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting

Signs and Symptoms of Hepatic Injury or Decompensation:

- Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark] (reflecting impaired bilirubin metabolism)
- More general signs and symptoms of ascites and encephalopathy: confusion, swelling of the legs or abdomen
- Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite
- Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea for more than 4 days) and should be an indication for prompt investigational product interruption and complete patient evaluation

Other Symptoms:

- Worsening of renal function or likely dehydration

Healthcare Provider (HCP) Interactions:

- Visits to primary HCP or referral to any specialist for any new symptoms (other than ongoing care for stable comorbidities)
- New medications or changes to current medications prescribed from HCP or any new over the counter medications or herbal supplements
- Laboratory procedures or assessments performed by an HCP

Signs and symptoms for potential hepatic injury or decompensation should be followed by (1) evaluation of liver biochemistry for suspected drug-induced liver injury (DILI) or potential hepatic decompensation (Section 7.4.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.4.3), (3) triggering of close monitoring or investigational product interruption/discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 13.1), and (5) contact with the Medical Monitor.

7.4.2. Liver Biochemistry Assessments for Potential Hepatic Injury or Hepatic Decompensation

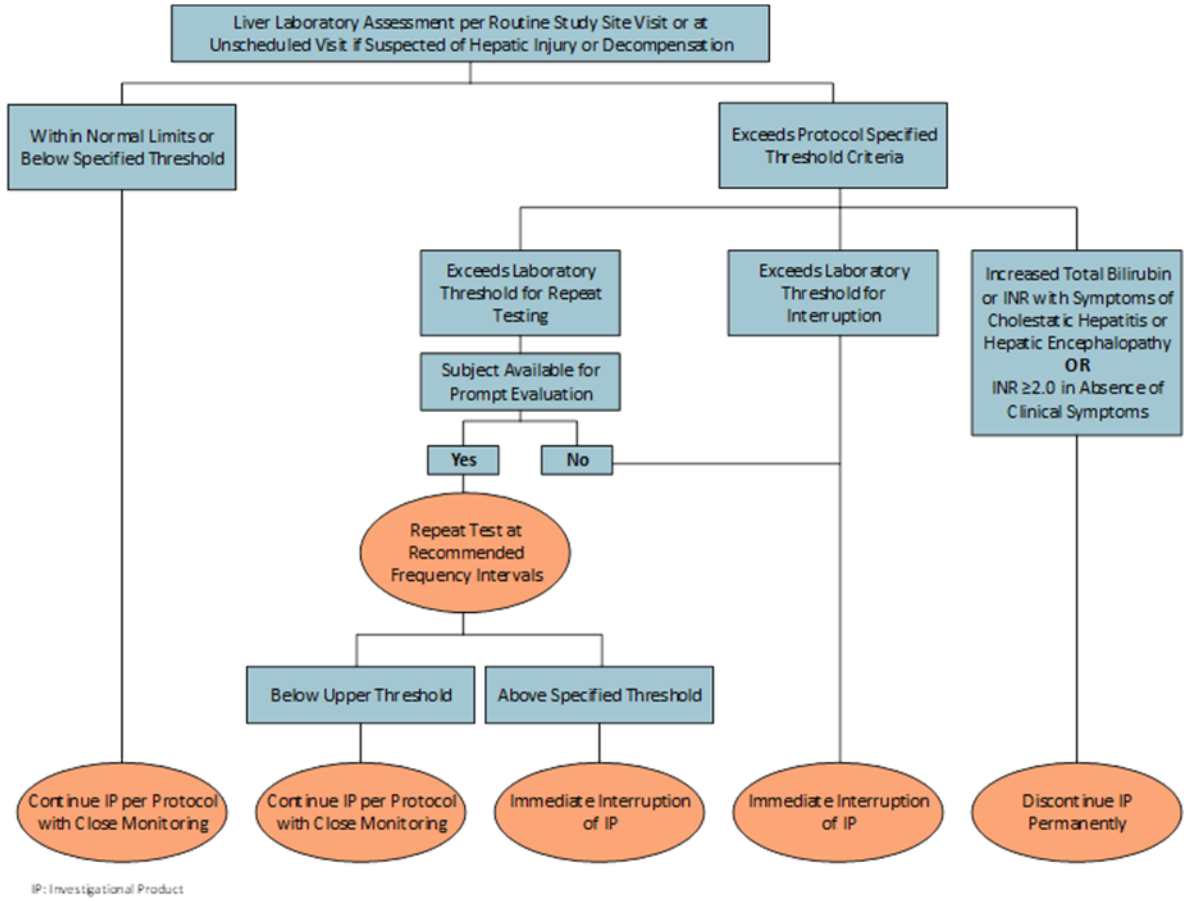
Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of patients for potential hepatic injury or hepatic decompensation. These assessments will be performed at:

- Each protocol-specified visit (Table 1)
- Unscheduled visits as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered

It is important that the laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. In the event that a patient cannot return to the clinic for a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local lab is permissible at the discretion of the Investigator. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges.

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and, potentially, a complete patient evaluation (depending on the repeat result) are summarized in Table 3.

Figure 2: DILI Management Algorithm



DILI = drug-induced liver injury; IP = Investigational Product

NOTE Other laboratory criteria include: ALT, AST, total bilirubin, INR, and electrolytes (sodium).

Table 3: Liver Laboratory Criteria for Monitoring of Suspected Hepatic Injury or Potential Hepatic Decompensation and Criteria for Interruption or Discontinuation of Investigational Product

A. Laboratory Criteria for Monitoring Suspected Hepatic Injury		
Laboratory Parameter	**Action Taken**	**Rechallenging Criteria**
Total Bilirubin		If a patient interrupts IP, they may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.
Baseline ≤ULN and ≥3x baseline	Interrupt IP	
Baseline >ULN and ≥2x Baseline	Interrupt IP	
ALT or AST		
>3x baseline (and >ULN)	Interrupt IP	
≥2x baseline	Repeat Test in 2 to 3 days, interrupt IP if still elevated	
Electrolytes[a]		
Sodium <130 mEq/L	Repeat Test in 2 to 3 days, interrupt IP if still below limit	
B. Laboratory Criteria for Monitoring Potential Hepatic Decompensation (Absence of Clinical Symptoms)		
Total Bilirubin	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt IP.	The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator. If laboratory values do not normalize, IP should not be restarted.
Baseline ≤ULN and 1.5 mg/dL increase from baseline Baseline >ULN and 1.0 mg/dL increase from baseline		
INR[b]		
>0.3 increase from baseline	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt IP.	The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator. If laboratory values do not normalize, IP should not be restarted.
≥2.0 unless due to vitamin K deficiency	Discontinue IP permanently	Continue to return for scheduled study visits for safety follow up. Monitor closely for clinical outcomes per protocol.
C. Laboratory Criteria for Monitoring Potential Hepatic Decompensation in the Presence of Clinical Symptoms		
Total bilirubin thresholds defined in Part B OR an INR increase from baseline of ≥1.5 are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy[c]	Discontinue IP permanently	Continue to return for scheduled study visits for safety follow up. Monitor closely for clinical outcomes per protocol.

IP = investigational product

[a] Sodium will be measured as an assessment of liver failure (hyponatremia).

[b] Does not apply in patients on anti-coagulants.

[c] Symptoms of cholestatic hepatitis includes dark urine and jaundice. Symptoms of hepatic encephalopathy may include lack of awareness, shortened attention span, lethargy, gross disorientation, or coma (unresponsive to verbal or noxious stimuli).

It should be noted that it is difficult to recognize every potential marker of hepatic or renal deterioration. There is no substitute for good medical judgment. Investigators will be reminded to be cautious and mindful in their evaluation of patients' symptoms, signs, and laboratory results. However, for example, a single abnormal laboratory analyte result may be artefactual; accordingly, Investigators will be allowed to implement an alternate follow-up procedure if considered appropriate based on their medical judgement, but only after documented agreement with the Sponsor's Medical Monitor.

7.4.3. Clinical Criteria for Monitoring for Potential Hepatic Decompensation

Patients will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 4.

Investigational product should be discontinued permanently if the patient received a liver transplant or experiences multi-organ failure as defined in Table 4, Part A. Patients should continue to return for scheduled study visits for safety follow-up.

Patients who experience other potential hepatic decompensation events defined in Table 4, Part B should be closely monitored until normalization or stabilization. Patients may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.

Table 4: Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Interruption / Discontinuation of Investigational Product

A. Hepatic Decompensation Events Requiring Mandatory Discontinuation of Investigational Product	
Decompensation Event	**Action Taken / Rechallenging Criteria**
Liver Transplant Multi-organ failure requiring hospitalization	Discontinue IP permanently and follow patients until normalization/stabilization. Continue to return for scheduled study visits for safety follow up.
B. Hepatic Decompensation Events Requiring Interruption of Investigational Product	
• Liver failure defined as worsening synthetic function that is persistently worse relative to baseline and/or progressive over time (see Table 3, Part B)[a] • Variceal bleeding or recurrent variceal bleeding[b] documented by endoscopy or accompanied by anemia or melena with a hemoglobin drop of ≥2 g/dL • Ascites[c] including: o Worsening – requires increase in drug therapy or surgical intervention (paracentesis or shunt procedure) o Refractory ascites – unresponsive to medication; patient not candidate for transjugular intrahepatic portosystemic shunt (TIPS) or shunt; requires large volume paracentesis o Hyponatremia (≤125 mEq/L) secondary to ascites • Spontaneous Bacterial Peritonitis • Hepatic Encephalopathy, Grade ≥2 • Any liver-related event requiring hospitalization and treatment (except multi-organ failure) • Hepatorenal syndrome Type 1 or Type 2 and acute kidney injury, hepatopulmonary syndrome, or portopulmonary syndrome	Closely monitor until normalization or stabilization. The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator IP should be re-initiated at a lower dose (or lower dose frequency) and titrated per Investigator discretion.

[a] Patients experiencing INR ≥2.0 unless due to vitamin K deficiency should be discontinued from IP permanently without rechallenge and should to return for scheduled study visits for safety follow up.
[b] Endoscopic confirmation of gastric or duodenal varices without evidence of bleeding should be closely monitored; investigational product may be interrupted at Investigator discretion
[c] New onset ascites requiring treatment should be closely monitored; investigational product may be interrupted at Investigator discretion

7.5. Dose Titration Criteria

Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns.

Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as assessed by a review of AEs and safety laboratory results). In general, down-titration may be done in response to tolerability concerns and can occur at any time.

Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated as defined in Section 7.3.

Scheduled Dose Titration - After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose for patients may occur no earlier than 6 weeks following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability).

7.5.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. To determine if a patient is eligible for a dose titration refer to Section 7.3.

7.6. Close Observation

If investigational product is interrupted or discontinued as described in Section 8.4, patients should be closely monitored (contacted by the site a minimum of every 2 weeks and scheduled visits every 6 weeks; if returning to the site for a scheduled visit is not feasible, use of a local lab may be permissible at the Investigator's discretion). At a minimum, the following assessments should be conducted at each study visit:

- Physical exam and thorough review of patient reported signs and symptoms,
- Liver biochemistry (including ALP, ALT, AST, GGT, total and conjugated bilirubin, creatinine, and albumin), prothrombin time (PT)/INR, serum electrolytes, and assessment of Child Pugh (only if the patient is at the study site) and MELD scores.

In addition, a trough pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any patient who develops an AE that is indicative of or consistent with hepatic injury or decompensation.

The following additional monitoring procedures should be performed for events of potential hepatic injury (per FDA Guidance for Industry on Drug Induced Liver Injury) or suspected hepatic decompensation based on criteria described in Section 7.4.1, Section 7.4.2, and Section 7.4.3. These cases need to be discussed with the Sponsor's Medical Monitor:

- Repeating liver biochemistry and function tests as described in Section 7.4.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic, as clinically indicated.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs potentially hepatotoxic, continued use of investigational

product should be discussed with the Sponsor's Medical Monitor. The patient may be discontinued from investigational product, if clinically appropriate.

- Obtaining a history of exposure to environmental chemical agents or herbal supplements which may be associated with liver toxicity.
- Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute HBV infection), and E; autoimmune or alcoholic hepatitis; Wilson's disease, hypoxic/ischemic hepatopathy; and biliary tract disease.
- Investigators should consider testing for Hepatitis E virus when assessing for hepatic decompensation as infection with Hepatitis E virus in patients with chronic liver diseases such as PBC may rapidly worsen with signs and symptoms similar to drug induce liver injury (Kumar 2013)
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Seeking hepatology consultation, if the Investigator is not a hepatologist

7.7. Criteria for Study Termination

The Sponsor (Intercept Pharmaceuticals, Inc.) reserves the right to terminate the study at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the Data Monitoring Committee (DMC), it may be necessary to stop the study before all patients have completed the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, Good Clinical Practice [GCP] noncompliance or poorly performing sites, as determined by the number of patients enrolled or the quality of the study data).

The Investigator and/or Sponsor (or designee) must notify the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of discontinuation of a site or the study and the reason for doing so.

Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all patients for the end of study (EOS) or end of treatment (EOT) Visit.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Population

This study will be conducted at approximately 35 international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B and CP-C. Prospective patients will be identified primarily from the hospital and/or physician's database of patients with PBC, or may be referred from other physicians. Patients may self-refer to an Investigator if they become aware of the study through local, national, or international PBC patient societies, forums, or networks.

8.2. Patient Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines [Lindor 2009, EASL 2009]), defined as having ≥2 of the following 3 diagnostic factors:
   - History of elevated ALP levels for at least 6 months
   - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
   - Liver biopsy consistent with PBC (collected at any time prior to Screening)
2. Evidence of cirrhosis including at least one of the following:
   - Biopsy results consistent with PBC Stage 4
   - Liver stiffness as assessed by TE Value ≥16.9 kPa
   - Clinical evidence in the absence of acute liver failure consistent with cirrhosis including: gastroesophageal varices, ascites, radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
   - Combined low platelet count (<140 000/mm^3) with:
     - persistent decrease in serum albumin, or
     - elevation in prothrombin time /INR (not due to antithrombotic agent use), or
     - elevated bilirubin (2× ULN)
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening:
   - Moderate: CP-B (Scores 7 to 9) or
   - Severe: CP-C (Scores 10 to 12)
4. MELD score of 6 to 24 at Screening
5. Age ≥18 years
6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate or unresponsive to UDCA (no UDCA for ≥3 months)
7. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) with spermicide **or** (b) diaphragm with spermicide; or

- Intrauterine device; or
- Vasectomy (partner); or
- Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
- Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)

8. Must provide written informed consent and agree to comply with the study protocol.

8.3. Patient Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. Current hepatic encephalopathy (as defined by a West Haven score of ≥2 [AASLD, EASL 2014])
5. History or presence of other concomitant liver diseases including:
   a. Hepatitis C virus infection and RNA positive
   b. Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the Medical Monitor
   c. Primary sclerosing cholangitis
   d. Alcoholic liver disease
   e. Definite autoimmune liver disease or overlap hepatitis
   f. Gilbert's Syndrome
6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function prior to randomization
7. Patients with history or presence of hepatorenal or hepatopulmonary syndrome
8. Patients with significant active infection (ie spontaneous bacterial peritonitis)
9. Patients with known or suspected hepatocellular carcinoma
10. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
11. Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study
12. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
13. UDCA naïve (unless contraindicated)

8.4. Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study

Investigational product may be temporarily decreased (eg, from 10 mg twice weekly to 5 mg twice weekly, or from 5 mg twice weekly to 5 mg once weekly) or temporarily or permanently stopped based on tolerability concerns. Investigational product may be resumed at the maintenance dose upon resolution of gastroenteritis or worsening renal function or dehydration if there is no evidence of liver injury. For rechallenge following all other dose interruptions (see Table 5), investigational product should be initiated at a lower dose and patients monitored more frequently with up-titration considered based on tolerability.

Adjustments, interruptions, discontinuation, and any rechallenge of investigational product should be implemented per the criteria outlined in Table 5. Patients that discontinue investigational product are expected to continue in the study (and follow the regular visit schedule, with the exception of PK sampling [trough PK may be required in the event of an AE consistent with hepatic injury or decompensation]) until the end of the study, but may withdraw consent at any time.

Table 5: Criteria for Dose Adjustment, Interruption, Discontinuation, and Rechallenge

DOSE ADJUSTMENT		
Criteria	**Action Taken with IP**	**Adjustment**
New Onset Severe Pruritus	Drug holiday or less frequent dosing	Return to original dose regimen if tolerated
DOSE INTERRUPTION		
Criteria	**Action Taken with IP[a]**	**Rechallenge[b]**
If liver biochemistries indicative of suspected hepatic injury are identified as exceeding upper threshold criteria and require immediate interruption (see Part A of Table 3)[c]	Interrupt immediately upon initial observation	Patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.
Other liver biochemistries indicative of suspected hepatic injury are outside upper threshold criteria upon repeat testing as defined in Part A of Table 3[d]	Interrupt after confirmation by repeat testing	
Liver biochemistries indicative of potential hepatic decompensation in the absence of symptoms (see Part B of Table 3)[e]	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt	
Clinical events indicative of hepatic decompensation (see Part B of Table 4)	Closely monitor until normalization or stabilization	The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator. IP should be re-initiated at a lower dose (or lower dose frequency) and titrated per Investigator discretion.

Gastroenteritis (established severe abdominal pain, vomiting, diarrhea for more than 4 days)	Interrupt	If no evidence of liver injury is detected, IP may be restarted at the same dose after resolution of intercurrent illness.
Evidence of worsening of renal function or dehydration	Interrupt	
DOSE DISCONTINUATION		
Criteria	**Action Taken with IP**	**Rechallenge**
If INR increases ≥2.0 in absence of clinical symptoms criteria (unless due to vitamin K deficiency) [f]	Discontinue / No Rechallenge	Discontinue IP permanently and continue to return for scheduled study visits for safety follow-up. Continue to return for scheduled study visits for safety follow-up. Monitor closely for clinical outcomes according to protocol assessments.
If total bilirubin thresholds (Part B of Table 3) are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy[f]		
Multi-Organ failure requiring hospitalization		
Liver transplantation		
Pregnancy		

Fully resolved = Return to baseline levels or return to within normal limits (WNL). IP = investigational product
[a] If patient is unable to be evaluated promptly, study drug must be immediately interrupted.
[b] Requires complete documentation of complete resolution or normal/baseline results based on laboratory parameters and symptoms.
[c] Total bilirubin baseline ≤ULN and ≥3x baseline, baseline >ULN and ≥2x baseline, ALT or AST >3x baseline (and >ULN)
[d] ALT or AST ≥2x baseline or electrolytes (sodium <130 mEq/L).
[e] Total bilirubin baseline ≤ULN and 1.5 mg/dL increase from baseline OR baseline >ULN and 1.0 mg/dL increase from baseline; INR >0.3 increase from baseline
[f] If INR increases ≥2.0 in the absence of clinical symptoms or if or total bilirubin thresholds OR an INR increase from baseline of ≥1.5 are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy.

8.4.1. Other Reasons for Discontinuation of Study or Investigational Product

The following events are considered appropriate reasons for a patient to discontinue investigational product; however, these patients are expected to continue in the study until study termination (or at the discretion of the Sponsor):

- Patient begins treatment with commercially available OCA.
- The Investigator or Sponsor considers that it is advisable or in the best interest of the patient.
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to study drug.
- Withdrawal of consent
  - Consent may be fully withdrawn (in which case the patient discontinues both investigational product and study visits and procedures).
  - Consent may be modified to discontinue study visits but allow semi-annual telephone contact.

- Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE) and liver-related clinical events.
- Early termination procedures should be conducted if the patient withdraws consent (see Section 9.7.13).

The Investigator is encouraged to contact the Sponsor prior to discontinuing a patient from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any patient prematurely withdraws from the study.

8.4.1.1. Withdrawal of Consent to Continue in the Study

If the patient decides that it is in his/her best interest to discontinue from the study, he or she may withdraw consent. It is fully understood that all patients volunteer for the study and that they may withdraw their consent to continue in the study at any time.

Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.13).

A reasonable effort must be made to determine the reason(s) for patient discontinuation. This information and date must be recorded in the appropriate eCRF.

8.4.1.2. Lost to Follow-Up

Patients will be considered "lost to follow-up" only after documented attempts to reach the patient prove unsuccessful. A reasonable effort (ie, 2 phone calls/messages, no response to registered letter) must be made to contact the patient and determine the reason(s) why a patient fails to return for a study visit or is lost to follow-up. This information and date of contact must be recorded in the appropriate eCRF.

8.4.2. Patient Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. This information must be documented in the eCRF.

If a patient is withdrawn from the study early (regardless of the cause), all of the early termination (ET)/EOS evaluations are to be performed at the time of withdrawal, to the extent possible.

9. TREATMENT OF PATIENTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or placebo.

Two treatment groups will be evaluated: OCA and placebo. Investigational product will be administered orally. Each dose will be made up of 1 tablet (ie, one OCA 5 mg tablet or one OCA 10 mg tablet, or matching placebo).

Investigational product will be taken orally with water for the duration of the study. Patients will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time on dosing days. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.2) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications (including prescribed, over the-counter, or herbal preparations) taken within 30 days of Screening and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 1.

PBC Specific Therapy

Investigators will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. Throughout the course of the study, Investigators are expected to monitor patients' PBC regimens and, if responsible for usual care, may adjust the regimen to achieve locally-appropriate treatment goals. These goals will be individualized, with the understanding that currently applicable PBC guidelines may vary across different geographic regions.

Ideally, patients should generally remain on the baseline PBC therapies throughout the course of the study, unless the baseline PBC therapy is no longer considered clinically appropriate by the Investigator. In addition, patients should be reminded to keep taking their blinded investigational product.

9.2.1. Drug Interactions

Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should not be taken within 4 hours of taking investigational product (and UDCA if applicable), ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration.

OCA taken concomitantly with warfarin may result in decreased INR levels; therefore, INR should be monitored and the dosage of warfarin adjusted, as needed during treatment with OCA and after cessation of OCA, to maintain the target INR range.

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate probe, showed weak effect of

OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

Information related to additional drug-drug interaction (DDI) studies is available in the current version of the IB. The aforementioned sections of the IB should be referred to during the course of the study, and are accessible to Investigators to help facilitate the assessment of potential DDIs with OCA that may be observed in study patients.

9.2.2. Prohibited Medications

Commercial OCA therapy (if available) is prohibited while on investigational product, and if prescribed during the course of the study, the Investigator should be cognizant of the possibility of double dosing. Patients who initiate with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.1).

9.3. Treatment Compliance

The Investigator should assess the patient's compliance with dosing of investigational product at each study visit, and confirm by conducting investigational product accountability (ie, count of returned tablets).

Patients should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the indicated visits (Table 1). The Investigator or designee should perform investigational product accountability (ie, count of returned tablets) and, if applicable, follow-up with the patient to retrieve any investigational product bottles that have not been returned.

If the Investigator has concerns about a patient's dosing compliance, he or she should discuss this with the patient, assess the reasons for noncompliance and the likelihood that the patient will remain noncompliant, and notify the Sponsor accordingly.

9.4. Randomization and Blinding

9.4.1. Methods of Assigning Patients to Treatment Groups

This study will be conducted in a double-blind, placebo-controlled manner. Enrolled patients who meet all eligibility requirements will be randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or OCA based on a predefined randomization code (generated by Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based patient registration system at Screening and Day 1.

Randomization will be stratified by CP class (CP-B or CP-C). Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores. The IWRS will serve as the investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the patient in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the patient to treatment. A randomization number will be assigned and investigational product (OCA or

placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind.

9.4.2. Blinding

The Sponsor, patients, Investigator, and study site staff will be blinded to the patient's treatment allocation during the patient's participation in the double-blind phase of the study.

9.4.3. Emergency Unblinding Procedures

Treatment assignment for individual patients will be made available to the Investigator for medical emergency use only (such as unblinding which is necessary in order to treat a serious adverse event [SAE] through the IWRS system). When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment assignment is necessary for further medical management of the patient). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the patient's record the rationale for unblinding and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment. Procedures for unblinding a patient's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual patient for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The DMC will have access to the IWRS and will be able to unblind individual patients. Refer to Section 15.8 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded patient data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the study is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DMC.

Access to treatment assignments will also be made available to the designated Intercept staff responsible for expedited safety reporting of suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

9.5. Assignment of Site and Patient Numbers

9.5.1. Site Numbers

Each study site selected to participate in this study will be assigned a site number by the Sponsor. The site number will be used to categorize patient data and to identify the site and/or Investigator within study documents. This number will be recorded in the eCRF.

9.5.2. Patient Numbers

Patients are assigned using a unique 10-character identifier (AAA-BBBCCC), independent of the randomization number. The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits represent the site number (BBB). The last 3 digits represent a unique screening number that is assigned in sequential order at each site starting with 001 (CCC).

9.6. Restrictions

Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited. Previous exposure to OCA (as a study participant or received commercial OCA therapy) is allowed provided patients haven't taken OCA within 3 months prior to enrollment in this study.

9.6.1. Fasting Requirement at Study Visits

All patients must have been fasting for at least 8 hours prior to their Screening Visit and all subsequent study visits, as all analytes will be assayed in fasting blood or plasma samples. Water is permitted during the fasting period.

9.7. Visit Procedures

9.7.1. Visit Windows

Visit windows are specified in the Schedule of Study Procedures (Table 1). Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. For example, Week 6 should ideally occur 6 calendar weeks (± 7 days) following Day 1.

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated informed consent form (ICF).

9.7.3. Assessing Cirrhosis

Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators:

- Biopsy results consistent with PBC Stage 4 (Ludwig 1978)
- Liver Stiffness as assessed by TE Value ≥16.9 kPa (Corpechot 2012)
- The presence of any of the following (unless exclusionary per Section 8.3) in the absence of acute liver failure:
  - Gastroesophageal varices
  - Ascites

  - Radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
- Combined low platelet count (<140 000/mm^3) with:
  - Persistent decrease in serum albumin, or
  - Elevation in prothrombin time /INR (not due to antithrombotic agent use), or
  - Elevated bilirubin (2× ULN)

9.7.4. Screening Procedures (14 days to 28 days prior to Day 1)

Informed consent must be obtained from the patient before performing any study-related procedures, including Screening procedures. The Screening Visit assessments must be performed ≥14 days but less than 28 days prior to Day 1 to determine whether the patient meets all the inclusion criteria and none of the exclusion criteria. Patients who do not fulfill all eligibility criteria will not be enrolled in the study. Patients may be rescreened after 2 months have elapsed from the date of their most recent screening visit procedure; however, all Screening procedures (including obtaining informed consent) should be repeated and a new three-digit Screening number assigned.

Screening Visit procedures are as follows:

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Collect medical history.
- Collect PBC history.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination, including height, smoking and alcohol consumption history, and current habits for both.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Perform a standard 12-lead electrocardiogram (ECG).
- Perform assessments for calculation of CP Score (Section 14.1.1)
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Virology Screen (HCV and HBsAg)

- Obtain urine sample for urinalysis
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test in females of childbearing potential.
- Instruct the patient to fast overnight (at least 8 hours) before the next visit (water is permitted).
- Record the visit in IWRS.
- Perform an ultrasound for HCC surveillance and evaluation of gallbladder status (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required. If the ultrasound cannot be performed at Screening (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed anytime within the screening visit window or on Day 1. Results from the screening ultrasound should be reviewed to assess possible exclusion criteria prior to randomization.

9.7.5. Day 1 Procedures (Randomization)

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Review inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant heath care professional (HCP) or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (Section 13.2.7).
- Randomize the patient only if s/he meets all inclusion criteria and no exclusion criteria.
- Record the visit in IWRS and dispense investigational product
  - Instruct the patient to begin dosing on the day of the Day 1 Visit.

- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of fibrosis (ELF [HA, P3NP, and TIMP 1])
  - Fasting PK assessment
  - Bile Acid/C4/FGF-19
- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.
- If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.6. Week 3 and Week 42 Safety Visit Procedures

Preferably, the patient will come in to the clinic for this visit. Alternatively, the site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.

- Verify that patient is dosing as directed.
- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Review and record prior concomitant medications.
- Assess and record AEs.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.

- Assess investigational product compliance, perform investigational product accountability.
- **For Week 42 Only:** Assess for dose titration, if eligible. (Refer to Section 7.3)
- **For Week 42 Only:** Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
- Schedule the next visit (Week 6 or Week 48), reiterate dosing instructions, and advise the patient:

  For Week 3 Only:

  - **Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose**, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3).
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

  For Week 42 Only:

  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.7. Week 6 Procedures

Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3).

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).

- Assess and record AEs.
- Review and record concomitant medications.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Bile Acids/C4/FGF-19
  - Fasting PK assessment
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.8. Week 9 through Week 48 (Safety Contact)

Patients should be contacted by telephone/email at Week 9 and every 3 weeks afterward to Week 48.

- Contact patient by phone/email.
- Review and record prior concomitant medications.
- Assess and record AEs.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.

9.7.9. Week 12, Week 24, Week 36 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible. (Refer to Section 7.3)
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of fibrosis (ELF [HA, P3NP, and TIMP 1])
  - Bile Acid/C4/FGF-19
  - Fasting PK assessment (**Week 36 only**)
- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit.
- Perform an ultrasound for HCC surveillance at **Week 24 ONLY** (if equipment is unavailable, sites should make every attempt to use available community referral sites).

- Serial PK assessment **at Week 12 and 24 ONLY (not done at Week 36)**; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose

Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.

- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to visits; s/he will dose at the clinic for Week 18 and Week 30 visits (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.10. Week 18 and Week 30 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.

- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Bile Acid/C4/FGF-19
- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose

Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.

- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to both visits; s/he will dose at the clinic on Week 24 (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.11. Week 48 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform ECG.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform urinalysis
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of fibrosis (ELF [HA, P3NP, and TIMP 1])
  - Bile Acids/C4/FGF-19
- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample

- Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water.
- Collect blood samples at: 30 min, 45 min, 1 hour postdose
- Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes)
- Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose

Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.

- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data are needed for cirrhosis assessment) or as close as possible to the visit.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit, and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.12. Every 3 Months after Week 48

Quarterly

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination, including height, smoking and alcohol consumption history, and current habits for both.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.

- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit, and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

Patients will complete a TE/ELF (HA, P3NP and TIMP 1) and ultrasound (for HCC surveillance) assessment, every 6 months (±2 weeks) after Week 48.

ECG and urinalysis will be done yearly (±2 weeks) after Week 48.

9.7.13. End of Study/Early Termination/End of Treatment Procedures for Patients That Withdraw from Investigational Product or Withdraw Consent

Patients who discontinue investigational product before Week 48 are expected to continue in the study until the end of the study (EOS [when patient terminates the study]) or at the discretion of the Sponsor.

EOT (when patient discontinues investigational product)/ET procedures will be required whenever patients discontinue treatment with investigational product (Table 1, Section 9.7.11). The EOT/ET Visit (Table 1) and procedures listed below (Table 6) must be performed as close as possible to the patient's last dose of investigational product. When a patient discontinues or interrupts investigational product and continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. The actual investigational product discontinuation scenario (Table 6) will determine the sequence of the EOT/ET and EOS Visits

and procedures. In some cases, the EOT/ET Visit and procedures will precede the EOS Visit; in others, the EOT/ET and EOS Visits will be combined and performed as close as possible to the patient's last dose of investigational product. EOT and EOS Visits are encouraged but at no time will a missed EOT or EOS visit be considered a protocol deviation.

When a patient ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (ET) (withdrawal of consent) or discontinuation, an EOT/EOS Visit must be performed as near as possible to her/his last dose of investigational product and the procedures listed in Table 1 performed. The purpose of this visit is to conduct complete and/or final assessments on or as near as possible to the final day of dosing. In some cases, the patient may discontinue on the day of a scheduled study visit. In these cases, EOT/EOS Visit procedures should be performed in place of the scheduled study visit procedures. The data will be recorded as EOT/ET and EOS procedures in the eCRF.

Table 6: Early Discontinuation Scenarios

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Early Termination	Discontinued	Withdrawn	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product.	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose of investigational product.	Complete at final study visit.
	Discontinued	Record review only	Record review only	Combined visit, completed as close as possible to last dose of investigational product.	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product.	
Pregnancy	Discontinued	Complete per the above scenarios - Early Termination or Treatment Discontinuation			
Lost to Follow-Up	Discontinued	LTF	None	Unable to complete due to LTF status	

EOS = end of study; EOT = end of treatment; LTF = lost to follow-up

[a] Refer to Section 7.1.2, Schedule of Study Procedures for all procedures and evaluations required at the EOS and EOT Visits.

[b] Includes initiation of commercially available OCA.

9.7.14. Unscheduled Safety Visit

The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted.

As appropriate, the Medical Monitor should be contacted.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

The investigational product is a white, round, film coated tablet containing OCA 5 mg or 10 mg or matching placebo. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

10.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to Good Manufacturing Practice standards by a designated qualified vendor. All investigational product will be provided as tablets for oral administration and provided in high density polyethylene bottles with heat induction seals and child resistant closures. The bottle packaging will not reveal any information about the treatment dose contained in the bottle. Multiple bottles may be dispensed to the patient at each visit to provide enough tablets for dosing until the next visit.

The designated investigational product packaging/distribution vendor will also be responsible for the distribution of the investigational product to the Investigator.

10.3. Investigational Product Storage

All OCA tablet strengths provided to clinical study sites in support of clinical studies are to be shipped and stored at 15°C to 25°C. Temperature excursions within the range of 2°C and 30°C for no more than a 6-month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20°C to 40°C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.

10.4. Investigational Product Administration

Refer to Section 9.1.

10.5. Investigational Product Accountability and Disposal

The Sponsor's representative will send investigational product to the study site under appropriate storage conditions. All shipments of investigational product should be unpacked and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product against the shipment documentation. The pharmacist or designee should contact the Sponsor immediately to report any concerns regarding the shipment.

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of investigational product accountability, including records of individual patient dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the Clinical Research Associate (CRA), will review accountability records against investigational product dispensed and that remaining in stock, during on site monitoring visits and when the study is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the investigational product. If the investigational product is to be returned to the Sponsor's vendor for destruction, the CRA will also prepare the investigational product for shipment.

11. OVERVIEW OF ASSESSMENTS

The assessments supporting the objectives for the study are in Table 7:

Table 7: Table of Assessments

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates glyco-OCA and tauro-OCA, and metabolite OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus, and fatigue
Secondary Objectives	**Assessments**
Changes in risk scores	Changes in MELD and in CP Scores and components of the CP score and MELD score
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma bile acids
Additional Objectives	**Assessments**
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	TE/ELF (HA, P3NP, and TIMP-1)
PK/PD relationship	PK parameters compared to PD parameters and safety and tolerability assessments (above)
Patient-reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
Clinical events	Death (all-cause and liver-related), liver transplant, MELD score ≥15 (for patients with MELD ≤12 at baseline), hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and HCC.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; INR = international normalized ratio; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PBC = Primary Biliary Cholangitis; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TE = Transient Elastography; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; VAS = visual analog scale

12. CLINICAL PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic analyses will be based on the PK population (Section 15.1). Patients in the PK Population with at least one PD assessment after dosing will be included in the combined PK/PD analyses.

12.1. Pharmacokinetic Blood Sampling

Serial and fasting PK assessments will be performed in all patients participating in the study.

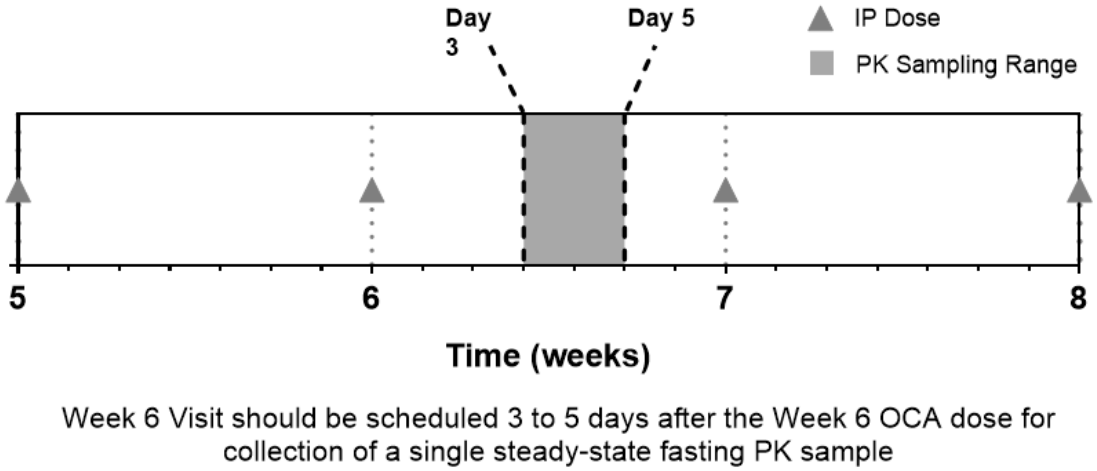
At Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48, patients will provide fasted blood samples for measurement of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide 30 minutes before administration of investigational product (Table 8). Patients will then receive a dose of investigational product with approximately 240 mL of water.

Week 6 Visit should occur 3, 4, or 5 days **after** the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure 3]).

During the treatment period:

- Pharmacokinetic fasting samples will be obtained from all patients at Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48 prior to dose administration in accordance with Figure 4.
- Serial PK assessments will be performed in all patients at Weeks 12, 18, 24, 30, and 48.

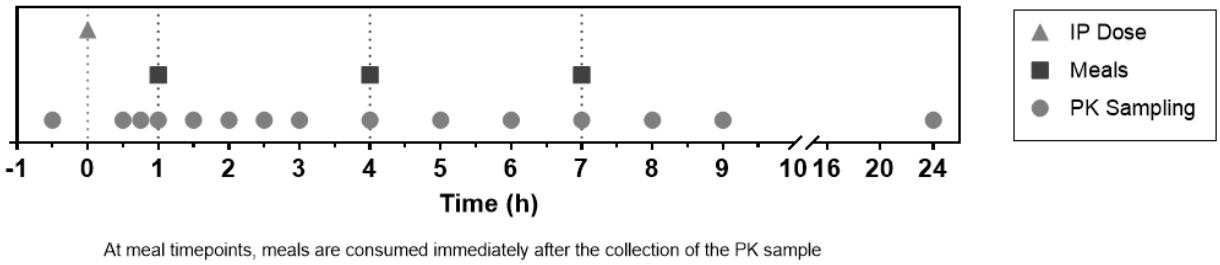
Figure 3: Week 6 Sampling Schedule



IP = investigational product; PK = pharmacokinetic

At Weeks 12, 18, 24, 30, and 48, serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose (Figure 4) for all patients. The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. The home health care agency must be advised one week in advance of the appointment.

Figure 4: Pharmacokinetic Sampling Schedule



h = hour; IP = investigational product; PK = pharmacokinetic

Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. The nutritional information of the meal replacement drink should be submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection.

Table 8: Acceptable Windows for Pharmacokinetic Sample Collection

Nominal Sampling Time	Acceptable Sampling Window
Before administration of investigational product (predose or fasting)	Within 30 minutes before dosing
0.5 to 1.5 hours after investigational product	± 10 minutes
2 to 2.5 hours after investigational product	± 20 minutes
3 to 24 hours after investigational product	± 30 minutes

12.2. Processing and Handling of Pharmacokinetic Samples

Whole blood will be collected at each scheduled sample timepoint. Detailed procedures for the collection of blood samples including further processing into plasma will be provided in a separate laboratory manual. The storage and shipment procedures for subsequent bioanalysis, will be provided to the investigational site and home health care company in a separate document before the study is initiated.

12.3. Bioanalysis

Plasma concentrations of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide will be determined using a validated liquid-chromatography mass spectrometry/mass spectrometry (LC/MS/MS) method. A detailed description of validation information and results from the bioanalytical assay will be provided in separate reports. These samples may be used for evaluation of metabolites of OCA or other concomitant medication, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by OCA.

13. ASSESSMENT OF SAFETY

13.1. Adverse Events and Serious Adverse Events

13.1.1. Definitions of Adverse Events

13.1.1.1. Adverse Event

AEs are defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to investigational product. An AE, also referred to as an adverse experience, can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) patient deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE.

Patients should be questioned about AEs in a general way, without leading the patient or asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

Patients should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as: pale-colored stools, urine color from pale to deep amber [dark], nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or the whites of eyes, and bruising easily.

13.1.1.2. Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

13.1.1.3. Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

13.1.1.4. Adverse Events of Special Interest

The following decompensation events are adverse events of special interest; a subset of these are also captured as additional efficacy assessments (see Section 14.2.3).

- Variceal bleeding or recurrent variceal bleeding documented by endoscopy OR patient presenting with anemia or melena (hemoglobin drop ≥2 g/dL) and found to have varices documented by endoscopy, irrespective of hospitalization or requirement of blood transfusion.
- Gastrointestinal bleeding as a result of gastric or duodenal varices verified by endoscopy
- Hepatic encephalopathy, Grade ≥2
- New onset ascites requiring treatment
- Worsening of ascites (requiring increase in drug therapy or requirement of surgical procedure such as paracentesis or shunt placement)
- Refractory ascites -unresponsive to medications, and patient is not a candidate for TIPS or shunt and requires large volume paracentesis
- Hyponatremia (Na ≤125 mEq/L) secondary to ascites
- Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis- by cell count/chemistry)
- Hepatorenal syndrome Type 1 and Type 2 and Acute Kidney Injury (AKI)
- Liver failure defined as worsening of liver synthetic function that is persistently worse relative to baseline and/or progressive over time:
  - Hepato-pulmonary syndrome
  - Porto-pulmonary syndrome
  - Liver Transplant
  - Increase in MELD scores by 3 points relative to baseline, persistent over time and unrelated to vitamin K deficiency related increase in INR

– Any liver related event that requires hospitalization and treatment

13.1.2. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 9. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as suspected adverse reaction (SAR). "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "definite," "probable," or "possible" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 9: Relationship of Adverse Events to Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; that is confirmed by stopping or reducing the dosage of the investigational product; and that could not be reasonably explained by the known characteristics of the patient's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product; that does not follow a known or suspected response pattern to the suspected investigational product; and that could reasonably be explained by known characteristics of the patient's clinical state.
Not Related	Any event that does not meet the above criteria.

13.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 10, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 10: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Causing no limitation of usual activities; the patient may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the patient may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

13.1.4. Reporting of Adverse Events and Serious Adverse Events

13.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the patient fully completes her/his study participation.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any patient.

13.1.4.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

All SAEs must be reported to the Sponsor (including suspected liver-related clinical outcome events that qualify as serious). SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by:

- E-mail to the SAE email address: PPD
- Fax using a paper SAE report form: PPD

If an SAE is reported by fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Patient number
- Event term
- At least 1 criterion classifying the event as serious

- Name and title of the reporting individual
- Causal relationship to the investigational product

The Investigator will assess whether the event is causally related to the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of Safety Reports/Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to PPD or emailed to PPD as soon as possible.

The Investigator is responsible for submitting information on Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local country requirements. Documentation of the submissions to IRBs/IEC s must be retained in the appropriate study file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate investigative site study files or with the IB.

13.1.5. Additional Investigator Responsibilities for SAEs

The safety data recorded in the EDC represent the official record of all AEs and SAEs reported in the study. The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the patient's AE eCRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Sponsor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for patient care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the Medical Monitor.

13.1.6. Notification of Post-Treatment SAEs for Patients Who Continue in the Study

Post-treatment SAEs that occur in patients who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2 .

SAEs that occur in patients who discontinue investigational product, initiate treatment with commercially available Ocaliva, and remain in the study must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

13.1.7. Notification of Post-Study SAEs

All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2.

13.1.8. Follow-Up of AEs and SAEs

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

Drug-Induced Liver Injury or Disease Progression

All patients showing possible drug-induced liver injury or disease progression should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

Cholecystitis or Pancreatitis

Patients should be instructed to contact the investigational site if they experience any of the following signs and symptoms: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, or weakness. Patients should also be counseled to seek immediate medical assistance if they experience persistent severe abdominal pain.

In the event that cholecystitis and/or pancreatitis is suspected, Investigators should promptly bring patients into the clinic to undergo a complete evaluation, including a physical examination, and laboratory assessments [ie, amylase and lipase]). Investigators should refer to standard of care guidelines on suspected pancreatitis (Banks 2012, Greenburg 2015). Diagnosis of acute pancreatitis includes 2 of the following:

- Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (or amylase) at least 3 times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging

To ensure appropriate vigilance, amylase and lipase levels should be monitored monthly for 3 months after onset of symptoms, irrespective of whether a diagnosis of cholecystitis and or pancreatitis is confirmed. The Investigator should contact the Medical Monitor upon awareness

of the above (ie, suspected or confirmed diagnosis). Results should be recorded promptly in the eCRF.

13.1.9. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when and AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 13.1.4 must also be followed.

13.2. Other Safety Parameters

13.2.1. Medical History/Demographics

A complete medical history will be obtained from the patient at screening. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

13.2.2. Medical and Surgical Procedures

Medical and surgical procedures will be recorded at the visits indicated in Table 1.

13.2.3. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the visits specified in the Schedule of Study Procedures (Table 1). A basic physical examination should be performed, including all body systems pertinent to the patient. Smoking and alcohol consumption history and current habits will be recorded. Any clinically significant abnormality should be reported on the AE eCRF page for findings that appear after consent, and on the medical history eCRF for any finding present prior to consent.

13.2.4. Vital Signs and Weight

Vital signs (oral temperature, sitting heart rate, respiratory rate and sitting blood pressure [BP]) and weight will be assessed at indicated visits (Table 1). When taking heart rate, respiratory rate and BP readings, patients should be seated quietly for a minimum of 3 minutes before the readings are taken.

13.2.5. Electrocardiogram

Standard ECGs will be collected at indicated visits (Table 1). The Investigator or designee will review the ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically

significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after Day 1 will also be documented as AEs and entered on the AE page of the eCRF.

Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time.

13.2.6. Laboratory Assessments

Patients will be instructed to attend each study visit in a fasted state, preferably in the morning, and patients should remain fasted until their blood samples have been collected. At all visits, the Investigator or designee will verify that the patient has fasted for at least 8 hours and record fasting status in the source and eCRF. If the patient reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and eCRF and remind the patient that fasting is required before all study visits.

Blood samples for serum chemistry, coagulation, and hematology; and urine samples will be collected at visits as detailed in the Schedule of Study Procedures (see Table 1). The number and volume of samples to be collected at each visit will be detailed in the laboratory manual.

Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

All patients with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.

Laboratory samples will be stored for a maximum of up to 1 year after the end of the study (depending on stability) in the event that retesting is required, and destroyed after 1 year if not analyzed.

The list of laboratory analytes to be tested is shown in Table 11.

Table 11: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen, creatinine, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, total bilirubin, free fatty acids, TFT (TSH, free T3 and free T4)
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)

Table 11: List of Laboratory Analytes to be Tested (Continued)

Laboratory Assessment	Analyte
Coagulation	PT, PTT, INR
Urinalysis; Pregnancy	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, leucocytes, nitrates; albumin, creatinine, albumin/creatinine ratio (if positive); β-hCG
Markers of Cholecystitis and Pancreatitis	Amylase and lipase
Noninvasive measurements of liver fibrosis	ELF (HA, P3NP, and TIMP-1)
PK assessments	OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)
PD markers	C4, FGF-19 and plasma bile acids

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = human chorionic gonadotropin; C4 = 7α-hydroxy-4-cholesten-3-one; CPK = creatine phosphokinase; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; HDL = high density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PT = Prothrombin time; PTT = partial thromboplastin time; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TG = triglyceride; TFT = thyroid function test; TIMP-1 = tissue inhibitor of metalloproteinase 1; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein

Laboratory reference ranges for the study will be based on the laboratory vendor range.

Urine based β-hCG pregnancy tests will be performed in female patients of childbearing potential per protocol specified visits (see Table 1). If a urine pregnancy test is positive, a serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified and the patient will be followed as outlined in Section 13.1.9 until pregnancy outcome.

INR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, and INR values, with modification by United Network for Organ Sharing. Total OCA will be calculated based on the sum of OCA, glycol-OCA, and tauro-OCA concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.

13.2.7. Patient-Reported Outcomes and Healthcare Resource Use

Data will be collected to determine the effects of OCA on health-related quality of life. Healthcare resource use as well as a general health status assessment (for the purposes of generating health utilities) will be used to support subsequent cost-effectiveness analyses that are relevant to major health care systems around the world. Assessments of patient-reported outcomes will take place during the visits indicated in Table 1.

The following patient-reported outcomes will be used to evaluate the effects of OCA compared to placebo on improvements in health-related quality of life:

- PBC-40: The PBC-40 is a validated disease-specific 40-question quality of life questionnaire, which consists of 6 domains: General Symptoms, Itch, Fatigue, Cognitive Function, Social, and Emotional (Jacoby 2005).

- EQ-5D-5L: The EQ-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VASs). The descriptive system is organized into 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the patient's self-rated health on a 20-cm vertical, line with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman 2011, Oemar 2013).
- Pruritus VAS: A VAS will also be used to assess pruritus in individual patients.
- Chronic Liver Disease Questionnaire: The CLDQ is a disease-specific health related quality of life questionnaire for patients with chronic liver disease. The questionnaire includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry). Each question is answered on a scale from 1 (always) to 7 (never) with a higher score corresponding to a better quality of life. The CLDQ produces a summary score and domain scores that correlate with the severity of liver disease (Younossi 1999).

Patients will be asked to complete the questionnaires and initial and date each document. The questionnaires should be filed in the patient's study records. These may require transcription to the eCRF by study site staff.

Healthcare resource use will be collected from eCRFs including number, reason for and duration of hospitalizations and emergency room visits, number of outpatient physician visits (patient reported), and use of concomitant medications. The purpose is to evaluate the effects of OCA compared to placebo on patient-reported outcomes and healthcare resource.

14. EFFICACY ASSESSMENTS

14.1. Biochemical Measures of Disease Severity

14.1.1. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory.

Table 12: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	µmol/L	<34	34-50	>50
	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	28-35	<28
	g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Mild	Moderate-Severe
Hepatic encephalopathy[a]		0	Grade 1 or 2	Grade 3 or 4

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
(Pugh 1973, Lucey 1997), Vilstrup 2014

14.1.2. Model of End Stage Liver Disease Score

The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is useful in assessing patients with significant decompensation, and the MELD score is now used by the United Network for Organ Sharing in the US and Eurotransplants to manage the organ allocation for liver transplantation. The threshold for placement on an organ transplantation queue varies between regions across the globe.

An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival (Kamath 2007). MELD score will be calculated and reported for visits where these parameters are measured (see Table 1).

14.1.3. Changes in Liver Biochemistry and Hepatobiliary Damage

ALP, ALT, AST, GGT, total and direct bilirubin, INR, creatinine, albumin, platelets will be measured according to the frequency listed in Table 1.

14.2. Additional Assessments

14.2.1. Noninvasive Measurements of Liver Stiffness and Fibrosis

The ELF test assesses: HA, P3NP, and TIMP-1. Samples will be assessed in patients according to the schedules presented in Table 1.

The Fibroscan® TE device (Echosens, Paris, France) will be used at all study sites that have the equipment to collect hepatic stiffness measurements. These study sites must have the staff trained in the use and data interpretation of the device. This is a validated and non-invasive radiological technique used to assess hepatic fibrosis which will be conducted according to the schedule presented in Table 1.

14.2.2. Markers of FXR activation

Blood samples will be collected in all patients to measure C4, FGF-19, and bile acids. The results of these analyses will be used to assess the PK/PD response of OCA. Blood samples will be assessed in patients according to the schedule presented in Table 1.

14.2.3. Clinical Outcome Events

Clinical outcome events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.

15. STATISTICAL METHODS AND ANALYSES

Individual patient data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by patient. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on treatment study days are numbered relative to the day of the first dose of investigational product which is designated as Day 1.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, Baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For continuous variables, the number of patients, mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more decimal place than the raw data, and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations.

There will be no formal hypothesis testing in this study. However, summary statistics for each treatment group will be presented, as well as 95% CIs for the difference between the treatment groups.

15.1. Analysis Populations

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

15.2. Determination of Sample Size

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. A total of 30 patients is adequate with 10 patients on placebo to be included as a comparator and 20 patients on OCA. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized in a 1:1 ratio to 1 of the 2 treatment groups: Placebo and OCA.

15.3. Pharmacokinetic Analyses

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, metabolite OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

PK analysis will be based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics. Full details regarding the planned analyses, methods, and outputs for the study will be detailed in the statistical analysis plan (SAP).

15.4. Safety Analyses

Safety analyses will be conducted using the Safety population. Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vital signs, ECG, and clinical laboratory results will be summarized by treatment group using the Safety Population.

The incidence of TEAEs and SAEs will be tabulated by system organ class (SOC) and preferred term (PT) for each treatment group, and similarly by severity and relationship to treatment.

Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized.

No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.

15.4.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs.
- Patient incidence of TEAEs and the total number of entries by MedDRA SOC and PT. This summary will be repeated for all subgroups.
- Patient incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Patient incidence of TEAEs by MedDRA SOC, PT, and closest relationship to investigational product (Related/Not Related). Related AEs are those with relationships reported as "Definite," "Probable," or "Possible," and unrelated AEs are those with relationships reported as "Unlikely" or "Not Related." At each level of patient summarization, a patient is classified according to the closest relationship if the patient reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Patient incidence of serious TEAEs and the total number of entries by MedDRA SOC and PT.
- Patient incidence of TEAEs leading to investigational product withdrawal or study discontinuation by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Patient Discontinued from Study" is checked.

The following listings will be presented by treatment group and patient:

- All adverse events.
- Serious adverse events (This is a subset of the AEs where serious is marked as "Yes").
- Severe adverse events (This is a subset of AEs where severity is marked as "Severe").
- Related adverse events (This is a subset of the AEs where relationship marked as "Definite," "Probable," or "Possible").

- Adverse events leading to Study Drug Withdrawal or Study Discontinuation (This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Patient Discontinued from Study" is checked).
- Adverse events leading to death (This is a subset of the AEs where the corresponding AE number is specified on the Death eCRF).

Adverse events of special interest as defined in Section 13.1.1.4 will be summarized for each treatment group.

15.4.2. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.

15.4.3. Additional Safety Analysis

Vital Signs and Weight

The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.

Electrocardiograms

Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.

15.4.4. Adverse Events of Special Interest

Pruritus: Treatment-emergent pruritus, defined as any PT including "Prur," will be summarized separately by the MedDRA SOC, treatment group, and PT as a subset of all TEAEs. This summary will be repeated for patients with "new or worsened" pruritus events, as defined as follows:

- Mild, moderate, or severe treatment-emergent pruritus events in patients with no pruritus at Baseline, or
- Worsening of the severity of the Baseline condition in patients with pruritus at Baseline.

Baseline pruritus is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose Baseline severity is severe will be counted as worsening if an AE of pruritus with severe is recorded.

An analysis of treatment-emergent pruritus event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between pruritus and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent pruritus
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Patients who never reported an AE of pruritus will be censored at the date of last contact.
- Time to onset of the first moderate or severe treatment-emergent pruritus
  - The time to the start of the first moderate or severe pruritus will be calculated by date of onset of the first moderate or severe pruritus – date of first dose of investigational product +1.
  - Patients who never reported a moderate or severe AE of pruritus will be censored at the date of completion or discontinuation.
- Time to onset of the first severe treatment-emergent pruritus
  - The time to the start of the first severe pruritus will be calculated by date of onset of the first severe pruritus – date of first dose of investigational product +1.
  - Patients who never reported a severe AE of pruritus will be censored at the date of completion or discontinuation.

The analysis of time to first onset of treatment-emergent pruritus AE, time to onset of the first moderate or severe treatment-emergent pruritus, and onset of the first severe treatment-emergent pruritus will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without pruritus (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The tabulation will include the KM estimate methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles of the medians and corresponding with associated 2-sided 95% confidence intervals (CIs), if the medians can be estimated as well as percentage of censored observations.

Fatigue: Treatment-emergent fatigue is defined as any PT which includes “Fatigue.” New or worsened treatment-emergent fatigue is defined as follows:

- Any mild, moderate, or severe treatment-emergent fatigue events in patients with no fatigue at Baseline, or
- Worsening of the severity of the Baseline condition in patients with fatigue at Baseline.

Baseline fatigue is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose Baseline severity is severe will be counted as worsening if an AE of fatigue with severe is recorded.

An analysis of treatment-emergent fatigue event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between fatigue and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent fatigue
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Patients who never reported an AE of fatigue will be censored at the date of last contact.
- Time to onset of the first moderate or severe treatment-emergent fatigue
  - The time to the start of the first moderate or severe fatigue will be calculated by date of onset of the first moderate or severe fatigue – date of first dose of investigational product +1.
  - Patients who never reported a moderate or severe AE of fatigue will be censored at the date of last contact.
- Time to onset of the first severe treatment-emergent fatigue
  - The time to the start of the first severe fatigue will be calculated by date of onset of the first severe fatigue – date of first dose of investigational product +1.
  - Patients who never reported a severe AE of fatigue will be censored at the data of last contact.

The analysis of time to first onset of treatment-emergent fatigue AE, time to onset of the first moderate or severe treatment-emergent fatigue, and onset of the first severe treatment-emergent fatigue will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without fatigue (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group.

15.5. Efficacy Analyses

This study does not plan to test a formal hypothesis for any efficacy endpoint.

The endpoints of efficacy assessments are change in total and direct bilirubin, INR, creatinine, albumin, platelets, ALP, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from

baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Summary statistics of the laboratory values will be provided by treatment group. The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 2-sided 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 2-sided 95% CI of the difference will also be presented.

Risk Scores: Changes from baseline in the MELD score and in CP score, C4, FGF-19 and plasma bile acids will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.

Shifts in MELD scores from Baseline will be reported by visit using the following categories: <10, 10 to <12, 12 to <13, 13 to <14, 14 to <15, and ≥15.

CP class will be presented in shift tables showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of patients within each shift classification.

Individual factors will be presented in a listing.

15.6. Additional Efficacy Analyses

Analyses of changes in liver stiffness (TE) and liver fibrosis (ELF [HA, P3NP, and TIMP-1]) will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin.

The following clinical endpoints will be captured in the study:

- Time to death (all cause)
- Time to liver-related death
- Time to liver transplant
- MELD score ≥15 (for patients with MELD ≤12 at baseline)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Time to variceal bleed
  - Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)

  - Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC) will be summarized by treatment group using the same methods as defined above.

Full details regarding additional efficacy analyses will be detailed in the SAP.

15.7. Handling of Missing Data

Missing data will be assumed to be missing at random. No data will be imputed.

15.8. Data Monitoring Committee

An independent DMC includes hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), and statistician(s) not involved in the study as Investigators, adjudication committee members, or consultants. The DMC will have oversight of the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the Food and Drug Administration (FDA) debarment list will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data in order to ensure the safe and proper treatment of patients. Based on review of these data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study.

Written minutes of both the open and closed DMC sessions will be prepared. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked.

Data listings provided to the DMC do not contain individual patient treatment information; however, the DMC will have access to the database and may unblind individual patient data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all patients and separate treatment columns with ‘dummy’ labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, and AEs leading to early withdrawal of

investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.

The DMC may agree to adjust meeting frequency based upon actual and projected safety and efficacy data availability. Adjustments to or stopping of the protocol defined doses may be considered based on DMC evaluation of OCA safety and tolerability.

All Investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to patient safety, which alter the conduct of this study. The Investigators will inform the patients of such actions and the protocol, PIS, and ICF will be revised, as appropriate.

15.9. Adjudication Committees

All suspected liver-related clinical events, major adverse cardiovascular events (MACE)/expanded MACE, and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 3 committees and event types they are responsible for adjudicating are as follows:

- Cardiovascular Adjudication Committee (CAC): Adjudicates all suspected MACE, including all deaths
- Hepatic Outcomes Committee: Adjudicates all deaths and suspected liver-related outcomes
- Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events

Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the suspected events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual patient treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

Study records at each site will be monitored at regular intervals by a representative of the Sponsor, the CRA. The role of the CRA is to aid the Investigator in the maintenance and documentation of complete, accurate, legible, well organized and easily retrievable data. In addition, the CRA will ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such must be given access to the patient's primary source documentation (eg, paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

The Investigator may exercise judgment in allowing the CRA access to particular sections of the patient's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

16.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IEC/IRB, and/or regulatory agencies to conduct one or more site audits during or after the study and agrees to allow access to all study-related documentation and information and be available for discussion about the study.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the Sponsor or designated personnel (eg, CRA), instruction manuals, data verification, cross checking, and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate collection of study data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the PIS-ICF and/or other patient information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to Intercept before he or she can enroll any patient into the study. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to study patients to the IRB/IEC for review.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. A favorable opinion on amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/ IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of SARs will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or its designee will provide reports to the IRB/IEC as requested, as a minimum annually, and after the study is complete.

18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, "(64th World Medical Association [WMA] General Assembly, Fortaleza, Brazil, October 2013),"and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

18.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated consent form must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the patient.

18.4. Patient Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

The Investigator will maintain a list of patient's names and identifying information (eg, patient's hospital number, unique patient number). This list will not be collected by the Sponsor.

The PIS-ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique patient number/randomization code/site number, only.

When personal data on patients are stored or processed by computer, the data must be protected to prevent disclosure to unauthorized third parties. The pertinent sections of the data protection laws in the country in which the protocol is being conducted will be complied with in full.

The PIS-ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, regulatory authorities, or IEC/IRBs may require direct access to parts of the hospital or study site records relevant to the study, including patient's medical history.

19. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the patients for the duration of the study. If the Investigator is not present in the study site during the assessment, he or she will leave instructions for the study site staff and a telephone number where he or she can be reached.

Named physician(s) will be responsible for the medical follow-up of patients, as applicable.

19.1. Adverse Event Reporting

The Investigator is responsible for recording AEs reported by the patient or discovered by any other means during the study. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

19.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the Investigator considers a patient's safety to be compromised if immediate action is not taken.

19.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

- Approved PIS-ICF (all versions)
- IRB/IEC approvals (of protocol/amendments, patient questionnaires, etc)
- Form FDA 1572
- Current medical license of Investigators
- Curriculum vitae of Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

19.4. Ethics Review (IRB/IEC)

Please see Section 18.1 for the Investigator's responsibilities regarding ethics review.

19.5. Archiving and Record Retention

The Investigator should retain all essential documents and correspondence relating to this study in the Investigator Site File (ISF). Any study documents stored elsewhere should have their location referenced in the ISF table of contents or in a note to file.

All documents relating to the study including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed study patient log and confidential patient identification list will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor before the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

20. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org).

Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include the following:

- Clinical Trial Registries (eg, www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (eg, basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions prior to the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data prior to the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.
- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
- Single Center Publication and Additional Publications: This is a multicenter study and is designed to be published with complete data from all the study sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter study and that the study was not intended, or statistically powered, for data presentation by a single study site.
- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this study to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to

represent its, or the Publication Committee's, opinion if these differ with the proposed publication.

- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and amendments, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

21. LIST OF REFERENCES

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APPENDIX A. SUMMARY OF CHANGES: PROTOCOL 747-401 VERSION 2 (DATED 22 MAY 2017)

Please note that Protocol 747 401 Version 1 was generated to specifically address US FDA post-marketing requirements but was not submitted to other Regulatory/Competent Authorities or Ethics Committees due to ongoing negotiations. The changes in Version 2 were incorporated based on FDA review of Version 1 of the protocol. In general:

- Background information was included to estimate the exposure difference between healthy subjects and patients with moderate hepatic impairment to support the rationale for dose selection (Section 5.4.2)
- Additional PK sampling times were added to adequately characterize the PK of OCA and its active metabolites at steady-state in patients with moderate and severe impairment when dosing weekly to biweekly (Section 12)
- The period between screening and Day 1 was extended to at least 14 days to establish a baseline for serum biomarkers with at least two samples two weeks apart (Schedule of Study Procedures, Section 9.7.4)
- The Week 3 contact Visit by email/telephone was changed to a Safety Visit to assess evidence of early hepatotoxicity (Schedule of Study Procedures, Section 9.7.6)
- Guidelines were added to assess patients for evidence of hepatotoxicity at each visit (Section 8.4.1.2).

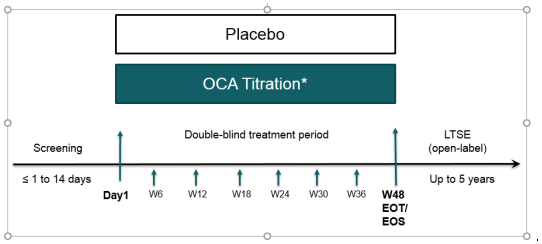
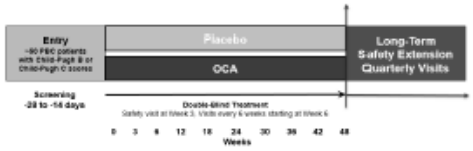
The table below includes substantial revisions made to Protocol 747-401 under Version 2. Revised text in Version 2 is indicated in bold font, and the text deleted from Version 1 is crossed out in the table below. (Minor/editorial changes and non-substantial changes are not listed individually in the summary table below).

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Title Page	~~**(For FDA Review Only)**~~	**EudraCT Number: 2017-001762-13**	Added EudraCT Number
STUDY PERSONNEL CONTACT INFORMATION	~~**Emergency Contact Information**~~ **Medical Monitor - ~~24-hour Emergency Reporting~~** Contact: PPD MD, Medical Director, ~~Drug Safety,~~ Intercept Pharmaceuticals, Inc. ~~Mobile:~~ PPD	**Medical Monitor** **Primary** Contact: PPD MD, Medical Director, **PI** Intercept Pharmaceuticals, Inc. (Intercept) Telephone: PPD Email: PPD	Updated contact list.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	Telephone: PPD Email: PPD ~~**Or if Not Available:**~~ ~~Contact:~~ PPD ~~, MD, PhD, Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~**SAE Contact Information**~~ ~~SAE Fax:~~ PPD ~~SAE email address~~ PPD ~~Telephone~~ PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD ~~VP, Clinical Operations, Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~Mobile:~~ PPD ~~Fax:~~ PPD ~~Email:~~ PPD	SAE Fax: PPD SAE Email: PPD	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	The study is planned to have approximately ~~20~~ investigational sites, globally	The study is planned to have approximately **35** investigational sites, globally	Updated site numbers.
Synopsis, Study Period, 7.1.3, Study Duration	Studied Period: ~~The study~~ will ~~include a 14-day screening period and a 48~~-week double~~-blind primary~~ treatment period. ~~Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete~~ the ~~primary treatment~~ period ~~at which point all~~ patients will ~~transition~~ to ~~an open-label long-term safety extension (LTSE).~~	Study Period: **Patients** will **receive double-blind treatment for at least** 48 **weeks. Patients who have completed their 48**-week **double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week** treatment period and the **database for** that period **is locked (approximately 3 years)**. Patients will **then be given the option** to **go on** open-label **treatment**.	Updated description of study period.
Synopsis, Objectives 6.1 Primary Objectives; 6.2 Secondary Objectives, 6.3, Additional Objectives,	: ~~In patients with Moderate to Severe PBC:~~ • To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and OCA glucuronide – Liver biochemistry including total bilirubin – … aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT – – Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF 19), 7α hydroxy-4-cholesten-3-one (C4), and plasma ~~and fecal~~ bile acids • To assess the PK/Pharmacodynamic (PD) relationship of OCA on: □ ALP, total bilirubin, ~~and aminotransferases~~ □ Bile acid homeostasis □ Safety and tolerability ~~(eg pruritus)~~	• To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and **metabolite** OCA glucuronide **compared with placebo** – Liver biochemistry including total **and direct** bilirubin – … aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT],), **international normalized ratio (INR), creatinine, albumin, platelets** – Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF 19), 7α hydroxy-4-cholesten-3-one (C4), and plasma bile acids • To assess the PK/Pharmacodynamic (PD) relationship of OCA with: □ **PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)**	Clarified study objectives.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	• To assess clinical ~~outcomes~~ consistent with end-stage liver disease	• **To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ])** • To assess clinical **events** consistent with end-stage liver disease	
Synopsis, Methodology and Section 7.1. Overall Study Design	Patients will be screened ~~for up to~~ ≤14 days…	Patients will be screened **≥14 days but not more than 28 days**…	Extended to 14 days to satisfy PMR for 2 baseline measurements.
Synopsis, Double-Blind Treatment Period, 7.1, Overall Study Design	Double-Blind ~~Primary~~ Treatment Period … (ie, Day 1 through Week 48), clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, ~~PK~~, and PD ~~(trough)~~. At each visit, ~~trough~~ PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12 ~~and only after a patient uptitrates~~. ~~Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the 48 week primary treatment period~~.	… Double-Blind Treatment Period: …(ie, Day 1 through Week 48), **an initial safety visit will occur at Week 3. After the Week 6, subsequent** clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. At each visit **(except screening and Week 3)**, **fasting** PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12, **18, 24, 30, and 48.** **Patients who have completed their 48-week double-blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. Patients will then be given the option to go on open-label treatment.**	Updated description of study period.
Synopsis, Long-term Open Label Extension Phase	~~Long-term Open Label Extension Phase~~ ~~Once all patients have completed the double-blind 48-week primary treatment period, patients will have the option to continue into an open-label long-term safety extension and all patients will receive OCA. Visits in the LTSE will occur every 3 months for up to 5 years. Patients on placebo during the primary treatment period will initiate study medication at 5-mg OCA once weekly and follow the dosing regimen based on their CP score. Patients on OCA~~	Section deleted.	Updated description of study.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~during the primary treatment period will continue the dose that they are on once unblinded.~~		
Synopsis and Section 7.1.1, Study Design Diagram	 ~~EOS = end of study; EOT = end of treatment,~~ OCA = obeticholic acid *Initial dose titration of investigational product ~~may occur at the Week 12 Visit, or any study visit~~ …	 **Note:** Initial dose titration of investigational product may **be considered as early as the Week 12 visit**, or any study visit thereafter for patients on all dosing regimens, based on …. **Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.**	Updated study diagram.
Synopsis, Dosing Regimen, Section, 7.3 (Table 2)	All patients will initiate investigational product once weekly with 5 -mg OCA or matching placebo. ~~Starting~~ at Week 12, ~~safety and tolerability of investigational product will be evaluated and,~~ ~~if tolerated, the patient can increase the dose to the next dose level as described below:~~ • ~~At Week 12~~, if investigational product is tolerated and laboratory assessments ~~from the Week 6 visit~~ do not indicate a safety concern, the patient ~~will change the dosing frequency~~ to 5 mg twice weekly, at least 3 days apart. • ~~Following an additional~~ 6 weeks ~~of treatment, if investigational product is tolerated,~~ patients ~~may be up-titrated to OCA~~ 10 mg twice weekly at least 3 days apart, the maximum dose for patients with CP-C. • Following an additional 6 weeks of treatment, if tolerated, Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, the maximum dose for patients with CP-B.	All patients will initiate investigational product once weekly with 5 mg OCA or matching placebo. **Titration may be considered as early as the Week 12 Visit. Following visit procedures** at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient **may up-titrate to OCA 5** mg twice weekly **and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur** at least 3 days apart. **Every** 6 weeks **thereafter, based on safety and tolerability assessments**, patients **can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.** Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily. **Patients with CP-C may titrate to a maximum dose of OCA** 10 mg twice weekly at least 3 days apart.	Updated table for clarity.

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr>
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• ~~If, during the course of the study, a patient transitions from CP- B to CP- C, or vice versa, the maximal dose for the new CP classification would apply.~~

Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score
<table>
<tr><th></th><th colspan="2">Child-Pugh B
(Moderate Hepatic Impairment)</th><th colspan="2">Child-Pugh C
(Severe Hepatic Impairment)</th></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose [a] (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>5 mg once weekly</td><td>matching placebo</td></tr>
<tr><td>Titration 1[b] ~~(≥Week 12)~~</td><td>5 mg twice weekly[c]</td><td>matching placebo</td><td>5 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 2[b] ~~(≥6 weeks after Titration 1)~~</td><td>10 mg twice weekly[c]</td><td>matching placebo</td><td>10 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 3[b] ~~(≥6 weeks after Titration 2)~~</td><td>5 mg once daily</td><td>matching placebo</td><td>NA</td><td>~~matching placebo~~</td></tr>
</table>
[a]~~Starting dose based on patient's Child-Pugh Score at Screening.~~

[b]Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.

[c]Dosing per the twice weekly schedule must be at least 3 days apart.
</td>
<td>
<table>
<tr><th></th><th colspan="2">Child-Pugh B
(Moderate Hepatic Impairment)</th><th colspan="2">Child-Pugh C
(Severe Hepatic Impairment)</th></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>5 mg once weekly</td><td>matching placebo</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo</td><td>5 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo</td><td>10 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 3[a]</td><td>5 mg once daily</td><td>matching placebo</td><td>NA</td><td>NA</td></tr>
</table>
[a]Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study

[b]Dosing per the twice weekly schedule must be at least 3 days apart.
</td>
<td></td>
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</table>

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td></td><td>(insertion)</td><td>If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply. If a patient demonstrates an improvement to CP-A, they should follow the dosing regimen for patients with CP-A.

Over the course of the study, a patient’s CP category may change. When a patient demonstrates a change in CP category, dosing should be reassessed and modified if appropriate. Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply. If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen should be followed.

Maximum Dose for OCA or Matching Placebo for Changes in Child-Pugh Category
<table><tr><th rowspan="2">Original Status</th><th colspan="3">New Status[a]</th></tr><tr><th>Child-Pugh A</th><th>Child-Pugh B</th><th>Child-Pugh C</th></tr><tr><td>Child-Pugh B</td><td>No change</td><td>No change</td><td>10 mg twice weekly[b]</td></tr><tr><td>Child-Pugh C</td><td>5 mg once daily</td><td>5 mg once daily</td><td>No change</td></tr></table>
[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for the planned dosing regimen.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.</td><td>Added to provide more information on dosing.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Synopsis and Section 8.2, Key Inclusion Criteria	2. Evidence of cirrhosis including at least one of the following: □ Biopsy ~~indicating cirrhosis or a medical history with histological evidence of cirrhosis~~ □ Clinical evidence consistent with cirrhosis including: ~~esophageal~~ varices, ascites, ~~encephalopathy,~~ or portal ~~hypertension~~ □ Liver stiffness as assessed by TE of ~~≥~~16.9kPa 6. ~~Age ≥18 years~~ 7. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate UDCA (no UDCA for ≥3 months) 8. ~~Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:~~ ~~– Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm, with spermicide; or~~ ~~– Intrauterine device; or~~	2. Evidence of cirrhosis including at least one of the following: • Biopsy **results consistent with PBC Stage 4** • Liver stiffness as assessed by TE **Median Value** ≥16.9 kPa • Clinical evidence **in the absence of acute liver failure** consistent with cirrhosis including: **gastroesophageal** varices, ascites, **radiological evidence of cirrhosis (nodular liver or enlargement** of portal **vein and splenomegaly)** • **Combined low platelet count (<140 000/mm^3) with** – **persistent decrease in serum albumin, or** – **elevation in prothrombin time/INR (not due to antithrombotic agent use), or** – **elevated bilirubin (2× ULN)** 6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate **or unresponsive to** UDCA (no UDCA for ≥3 months)	Provided more details regarding inclusion requirements. Only listed inclusions directly related to PBC in synopsis. Other criteria were deleted from synopsis but remain in the main body. Only criteria with changes are presented in this SOC. The full inclusion/ exclusion list is in the body of the protocol.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	– ~~Vasectomy (partner), or~~ – ~~Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection, or~~ – ~~Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)~~ 9. ~~Must provide written informed consent and agree to comply with the study protocol.~~		
Synopsis and Section 8.3, Key Exclusion Criteria	4. History or presence …: – Hepatitis C virus infection RNA positive 5. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function~~ during the Screening period~~ 6. ~~Patients with history or presence of hepatorenal or hepatopulmonary syndrome~~ 7. ~~Patients with significant active infection (ie spontaneous bacterial peritonitis)~~ 8. ~~Patients with known or suspected hepatocellular carcinoma~~ 9. ~~History of known or suspected clinically significant hypersensitivity to OCA or any of its components~~ 10. ~~Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study~~	4. **Hepatic encephalopathy (as defined by a West Haven score of ≥2)** 5. History or presence …: – Hepatitis C virus infection **and** RNA positive 6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function~~-~~**prior to randomization**	Added additional **key** exclusion criteria #4. Other criteria were deleted from synopsis but remain in the main body. Only criteria with changes are presented in this SOC.

Section	Original Text (Version 1, 20 Dec 2016)		Revised Text (Version 2, 22 May 2017)		Key Change
	11. ~~Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain~~ 12. ~~UDCA naïve (unless contraindicated).~~				
Synopsis, Duration of Treatment	~~The study will include a 14-day screening period and a 48 week double-blind primary treatment period. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the double-blind 48-week primary treatment period. Hence, depending on the rate of patient enrollment, patients will be exposed to investigational product for a minimum of 1 year up to approximately 2 years during the blinded period. Following completion of the blinded period, Patients will have the option to continue into an extension during which they will receive open label treatment and be seen at regular visits every 3 months for up to 5 years.~~		**Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment.**		Updated description of study.
Synopsis, Criteria for Evaluation and 11, Overview of Assessments, Table 5, Additional Objectives	~~PD Parameters;~~	plasma, ~~fecal~~ bile acids	**PK**	**Plasma concentrations of OCA and its conjugates, glyco-OCA, tauro-OCA; and metabolite OCA glucuronide**	Clarified study parameter for evaluation.
	Changes in MELD and in CP score		Changes in MELD and in CP score **and components of the CP score**		

Section	Original Text (Version 1, 20 Dec 2016)		Revised Text (Version 2, 22 May 2017)		Key Change
	PD parameters	f~~ecal~~ bile acids	**PK**/PD parameters	bile acids	
	Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30, ~~and others as determined during course of study.~~		IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30,	
	~~PK/PD relationship of OCA and liver biochemistry~~	~~OCA and its conjugates, glyco-OCA tauro-OCA; and OCA glucuronide~~	PK/PD relationship	**PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)**	
	~~PK/PD relationship of OCA and bile acid homeostasis~~	~~Bile acids~~			

Section	Original Text (Version 1, 20 Dec 2016)		Revised Text (Version 2, 22 May 2017)		Key Change
	Clinical ~~Outcomes~~	Incidence and time to first occurrence of any of the following: all-cause mortality, liver-related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, ~~hepatocellular carcinoma~~	Clinical **Events**	Death (all-cause and liver-related), liver transplant, Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline), Hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, Uncontrolled ascites, and HCC.	
Synopsis, Statistical Methods, Safety Analyses	The absolute change from baseline will also be summarized. No inferential comparison ~~of safety endpoints~~ will be performed.		The absolute change from baseline will also be summarized. No inferential comparison **with formal statistical hypothesis testing** will be performed **for safety endpoints.**		Clarified statistical methods.
Synopsis, Statistical Methods, Additional Efficacy Analyses	The following clinical ~~outcomes~~ will be captured in the study: • ~~All~~ cause ~~mortality~~ • Liver related death • Liver transplant		The following **endpoints consistent with end-stage liver disease** will be captured in the study: • **Time to death** (all cause) • **Time to** liver-related death • **Time to** liver transplant		Clarified statistical methods.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	• Variceal bleed • Hepatic encephalopathy • Bacterial peritonitis • ~~Ascites~~ • ~~Hepatocellular carcinoma~~ The incidence and time to first occurrence of any of the above listed clinical outcomes will be summarized ….The tabulation will include the KM ~~estimate of the medians~~ and corresponding 95% confidence intervals (CIs), ~~if the medians can be estimated~~. … The hazard ratio and 95% CI will be estimated based on a Cox regression model stratified by randomization strata. In addition, the incidence and time to each of the above ~~outcomes~~ -will be summarized by treatment group using the same methods as defined above.	• **Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)** • **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:** – **Time to** variceal bleed – **Time to** hepatic encephalopathy **(as defined by a West Haven score of ≥2)** – **Time to spontaneous** bacterial peritonitis **(confirmed by diagnostic paracentesis)** • **Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)** The incidence and time to first occurrence of the above listed clinical outcomes will be summarized ….The tabulation will include the KM **methodology using 25th, 50th (median),** and **75th percentiles with associated 2-sided** 95% confidence intervals (CIs), **as well as percentage of censored observations**. …. The hazard ratio and **2-sided** 95% CI will be estimated based on a Cox regression model stratified by randomization strata. In addition, the incidence and time to each of the above **clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC)** will be summarized by treatment group using the same methods as defined above.	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Synopsis and Section 15.2, Sample Size,	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients per OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. ~~The assessment was based on 80% powering for the 90% confidence interval of the geometric mean ratio of Total OCA (sum of OCA, glyco OCA, and tauro OCA).~~	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. **An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.**	
5.2, Nonclinical Experience with Obeticholic Acid	Insertion	**Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.**	Added section to briefly address nonclinical studies.
5.3, Clinical Development of Obeticholic Acid	As of 31 Jan 201~~6~~, approximately ~~1726~~ patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ patients had PBC, ~~330~~ patients had nonalcoholic steatohepatitis, 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease, 33 patients had alcoholic cirrhosis/portal hypertension, ~~and 20~~ patients had primary sclerosing cholangitis (PSC).	As of 31 Jan 201**7**, approximately **2186** patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** patients had PBC, **686** patients had nonalcoholic steatohepatitis (**NASH**), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (**NAFLD**), 33 patients had alcoholic cirrhosis/portal hypertension**,** **52** patients had primary sclerosing cholangitis (PSC), **and 5 patients had biliary atresia.**	Updated numbers of patients who have received OCA.
5.4, Rationale for Study Design and Dose for Investigational Product		**5.4 Rationale for Study Design and Dose for Investigational Product**	Inserted new header for clarity
5.4.1, Rationale for Study Design	~~Patients with moderate or severe hepatic impairment (Child Pugh B or C) will constitute approximately 20% of the patients included in the ongoing clinical outcomes Study 747 302 which was~~ specifically designed to confirm clinical benefit across the spectrum of disease including patients	**The 747-401 study is** specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment**.** Data collected from Study 747 401 will serve as a bridge to the **747-302 study.**	Clarified the intent of the 401 study.

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	with hepatic impairment. Data collected from Study 747 401 will serve as a bridge ~~between~~ the ~~two studies.~~		
5.4.2, Rationale for Obeticholic Acid Dose and Duration	~~Results from the hepatic impairment study (747-103) indicate that plasma exposure increases, in comparison to subjects with normal liver function, with increasing severity of impairment as classified by Child Pugh A (CP-A), CP-B or Child Pugh C (CP-C) scores by 1.4-, 8.0-, and 13-fold, respectively. No apparent impact on the overall safety profiles were observed in this study. Liver exposure, however, modestly increased by 1.1-, 1.5, and 1.7-fold, respectively, as shown in simulations using a physiologic PK model developed to characterize OCA and its conjugates.~~ Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure. (insertion)	**Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (CP Score). Model simulations predicted that for mild (Child-Pugh A [CP-A]), moderate (Child-Pugh B [CP-B]), and severe (Child-Pugh C [CP-C]) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to patients with normal hepatic function, whereas total OCA liver concentrations increase 1.1-, 1.5-, and 1.7-fold, respectively. Because the liver is the primary site of action for the safety and efficacy of OCA, it is important to account for the differences in systemic and liver exposure when assessing effective doses. It is also important to note that while hepatically impaired (CP-B and C) patients treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy patients, no apparent impact on the overall safety profile was observed, consistent with only a modest increase in liver exposure of OCA associated with hepatic impairment. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.** **Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower**	Added rationale for OCA dosing in hepatically impaired patients.

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	Therefore, a modified dosing regimen is recommended for OCA in patients with moderate and severe hepatic impairment that is designed to initiate doses to achieve plasma exposures levels of OCA similar to those without hepatic impairment or CP-A. After which, subjects may then titrate their doses upwards to achieve liver exposures that would be similar in both patient populations. ~~This modified dosing regimen was selected based on the established safety and tolerability of OCA in subjects with PBC, along with PK/PD modeling and simulations.~~ ~~Patients will initiate dosing at OCA 5 mg once weekly. Starting at Week 12, if the prior dose regimen was tolerated, the patients will increase the dosing frequency to 5 mg twice weekly (at least 3 days apart). After 6 weeks, a second titration may occur to OCA 10 mg twice weekly as long as tolerated. Patients classified as CP-B may further titrate their dose upwards to OCA 5 mg once daily after 6 weeks on the OCA 10 mg twice weekly regimen.~~	**dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).** **The dosing regimen in this study follows the FDA-approved prescribing information, with the exception of the maximum allowed dose in patients with moderate impairment. While the prescribing information allows for a maximum dose of 10 mg twice weekly for patients with moderate impairment, the protocol allows for a maximum dose of 5 mg once daily. The choice of 5 mg once daily is supported by the estimated steady-state liver and plasma exposure of total OCA for patients with moderate hepatic impairment receiving a 5 mg once daily dose relative to healthy patients receiving a 10 mg dose. A maximum allowed dose of 5 mg once daily in patients with moderate hepatic impairment is estimated to achieve liver exposure similar to non-hepatically impaired patients receiving a 10 mg daily dose and maximize efficacy in this patient population.**	
7.1.2, Schedule of Study Procedures	Schedule of Study Procedures ~~(Double-Blind Treatment Period)~~	Schedule of Study Procedures	Updated procedures to match updated study design.
7.1.2, Schedule of Study Procedures, Visit Windows	~~≤ 1~~ to -14 days	**-28** to -14 days	Updated procedures to match updated study design.
7.1.2, Schedule of Study Procedures, Visit Weeks Row	Week 3: ~~Safety Contact~~ Week 48 Under Long-Term Treatment	Week 3 Week 48/**ET/EOS/EOT** **Every 3 months**	Week 3 telephone/email contact visit now a

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			laboratory safety visit.
7.1.2, Schedule of Study Procedures	(Insertion) Dose Titration IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30, ~~others as determined during course of study~~ ~~Fecal PK Analysis~~ ~~TE Fibroscan®~~ ELF ~~MELD~~ PK ~~trough~~ Collection	Column: **Long-Term Treatment** Procedures: **Medical and Surgical Procedures** Dose Titration **Assessment** **Markers of Inflammation:** IL-6, hs CRP, TNF-α, IgM, IgG, IgA, CK-18-M30 • **TE**/ELF **(HA, P3NP, and TIMP 1)** PK **Fasting** Collection	Updated procedures to match updated study design
7.1.2, Table 1, Schedule of Study Procedures Footnotes	~~a~~ Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 3 and continuing to Week 48 to assess for AEs, concomitant medications, and verify that s/he is dosing as directed. ~~b Visits should be based on Day 1.~~ ~~c~~ The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits ~~(except Screening Visit 1)~~ but water is permitted. ~~d Medical history performed at Screening only.~~ ~~e The yearly physical exam will also include an~~ assessment of smoking and alcohol consumption history and current habits ~~for both~~. ~~Height~~ will ~~only~~ be collected at Day 1 and Week 48. ~~f~~ Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF. ~~g~~ The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated	**aVisit schedule should be based on Day 1. Day 1 visit must occur at least 2 weeks after screening visit.** [b]**Patients** should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week **9** and continuing to Week 48 to assess for AEs, concomitant medications, **medical/surgical procedures**, and verify that s/he is dosing as directed. [c] **Preferably, the patient comes in to the clinic for this visit. Alternatively, site will telephone the patient for assessments and home health nurse will visit to draw safety labs.** [d] **Visit should occur 3, 4, or 5 days after taking the Week 6 dose.** **e** The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, **including screening**, but water is permitted. f **Height and** assessment of smoking and alcohol consumption history and current habits will be **assessed** at **Screening** and Week 48. **Assessment of smoking and**	Updated procedures to match updated study design

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	translation is not available in the local language required for a specific study patient, the ~~data from that~~ questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease. ~~h~~ Patients will be instructed to begin dosing on the Day 1 visit after completing all study assessments. ~~(ie, on Day 1~~). Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet. ~~i~~ ~~Initial~~ dose titration of investigational product may occur at the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score. j Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally)	**alcohol consumption history and current habits will be assessed quarterly after Week 48.** g Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF. h The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease. **i New investigational product bottles will be dispensed if the patient is titrated. Unless up-titrated, patients are expected to use up each investigational product bottle before a new bottle will be dispensed. No new bottles will be dispensed if dose frequency is changed**. Patients will be instructed to begin dosing **on Day 1**, after completing all study assessments. Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet. **j** Dose titration of investigational product may occur starting **after the** Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score. **k** Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit **(except Week 3**). If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally).	

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		l The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling. **m The noninvasive radiological liver fibrosis measurement devices (such as, FibroScan® device [Echosens; Paris, France]) will be used at all study sites to collect hepatic stiffness measurements.** **n Patients will complete a TE/ELF and ultrasound assessment, every 6 months (±2 weeks) after Week 48.** **o ECG and urine dipstick will be done yearly (±2 weeks) after Week 48 Visit.** **p Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm suspected HCC.**	
7.1.3, Study Duration	~~The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the primary treatment period, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete the primary treatment period (Figure 1). Patients will have the option to continue into an open-label LTSE after all patients have completed the Week 48 procedures in which they will receive open-label treatment and be seen at regular visits every 3 months for up to 5 years.~~	**Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment**.	Updated description of study period.

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7.3, Planned Dosing Regimen	All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. ~~Starting~~ at Week 12, ~~safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below (Table 2):~~ • ~~At Week 12,~~ if investigational product is tolerated and laboratory assessments ~~from the Week 6 visit~~ do not indicate a safety concern, the patient will ~~change the dosing frequency to~~ 5 mg twice weekly, at least 3 days apart. ~~Following an additional 6 weeks of treatment, if investigational product is tolerated, patients may be up titrated to OCA~~ 10 mg twice weekly at least 3 days apart, ~~the maximum dose for patients with CP-C~~ ~~Following an additional~~ 6 weeks ~~of treatment, if tolerated~~, patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, ~~the maximum dose for patients with CP-B~~.	All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. **Titration may be considered as early as the Week 12 visit. Following visit procedures at** Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient will **up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur** at least 3 days apart**. Every 6 weeks thereafter, based on safety and tolerability assessments, patients can be considered for further up titration as described below (Table 3). At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.** **Patients with CP-C** may titrate **to a maximum dose of** OCA 10 mg twice weekly at least 3 days apart. Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.	Clarified dosing regimen.
7.4, Dose Adjustment Criteria, Scheduled Dose Titration	~~The first dose titration for any patient may occur no earlier than 12 weeks following~~ initiation of OCA or matching placebo.	**After** initiation of OCA or matching placebo, **titration may be considered as early as the Week 12 visit.**	Clarified dosing regimen.
7.4.1, Pre-Titration Tolerability Assessment Requirements	Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. ~~A review of AEs and available safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within approximately 6 weeks of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigational product (eg, Week 6, laboratory results should be reviewed prior to titration at Week 12). If for any reason, laboratory results are not available at the time of the~~	Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. **To determine if a patient is eligible for a dose up-titration refer to Section 7.3**	Clarified dosing regimen.

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	~~planned up titration visit, additional laboratory samples must be obtained and reviewed, prior to up titrating the patient to a higher dose. 7.3~~ ~~To be eligible for a dose up titration, patients should not be experiencing significant AEs that are suspected to be related to investigational product (eg, severe pruritus) or displaying other symptoms that may indicate intolerability of investigational product.~~		
7.4.2., Safety Criteria for Adjustment or Stopping Doses	~~Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.~~ ~~Subjects who discontinue investigational product are expected to continue in the study (and follow the regular visit schedule) until the end of the study, and the study will only terminate at the time.~~		This information has been incorporated into Section 8.4, which was renamed 8.4. Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study and additional text was added.
8.4, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	8.4 ~~Patient~~ Withdrawal ~~Criteria~~ (Insertion)	**Dose Adjustment, Interruption, and** Withdrawal **from Investigational Product or Study** **Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.**	Section revised to integrate withdrawal criteria in one section of protocol. Text was

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		Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling, but may withdraw consent at any time.	previously in Section 7.4.2.
8.4.1. Reasons for Additional Monitoring or Mandatory Interruption of Investigational Product	8.4.~~1~~. Reasons for Mandatory Discontinuation of Investigational Product	Moved to 8.4.**2** 8.4.1. Reasons **for Additional Monitoring** or Mandatory Interruption of Investigational Product	Heading text updated.
8.4.1.1, Reasons for Additional Monitoring Related to Liver Chemistries	8.4.1.1. ~~Pregnancy~~	8.4.1.1. **Reasons for Additional Monitoring Related to Liver Chemistries** **Patients who develop ALT or AST >2x baseline (and >ULN) or total bilirubin >1.5x baseline (and >ULN) should have repeat testing within 48 to 72 hours to confirm values. Patients with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or INR with persistent increases in ALT or AST should also be closely monitored.**	Pregnancy moved to Section 8.4.1.3. New Section with text added.
8.4.1.2. Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	(Insertion)	8.4.1.2. **Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries** **Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3× baseline (and >ULN)** • **Total bilirubin >2× baseline (and >ULN)** **Repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing should be performed. Detailed adverse event information should also be collected, and the patient should be investigated for possible causes of the liver chemistry changes, as appropriate. The Investigator**	New Section added to meet PMR requirements.

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		should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable. **If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), patients should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms.** **For the purposes of this protocol, if the above referenced significant elevation in liver enzyme or bilirubin levels resolve following interruption of investigational product and no other cause for the elevation is identified, the elevations should be assumed to be related to investigational product and investigational product should be discontinued. If the liver enzyme or bilirubin levels do not resolve following interruption of investigational product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the patient may be re-challenged following a discussion between the Investigator or designee and the Sponsor.** **Elevation of liver enzymes or bilirubin is based on comparison to baseline values defined as the mean of all available Screening and Day 0 values, which are the mean of all available evaluations prior to the first administration of investigational product. At least 2 of these samples will be obtained a minimum of 2 weeks apart during the Screening period. Elevations that occur gradually over the course of the study may be indicative of disease progression and should be assessed as clinically appropriate. Liver enzyme and bilirubin elevations that occur over a shorter time, such as within a 6-month period, should be evaluated for drug-induced liver injury as provided in the guidelines below.**	

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		If at any time a patient develops signs or symptoms of hepatotoxicity such as new onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>7%) in combination with elevations in liver enzymes, investigational product should be interrupted and liver enzymes monitored until signs or symptoms resolve. **Patients who develop evidence of severe drug-induced liver injury that is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged. Severe drug-induced liver injury includes, but is not limited to, functional hepatic impairment, as indicated by rising bilirubin or INR that cannot be explained by progression of disease. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.** **If after all investigations and actions outlined above have been completed, the investigator determines that the elevations in liver biochemistries are considered not related to investigational product, the Sponsor must be contacted before investigational product can be reinitiated. Follow-up procedures for patients resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment. Results must be reported to the site as soon as possible so the Investigator can determine if it appropriate for the patient is to continue treatment.** **The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.** **All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 15.9)**	

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8.4.1.3, Pregnancy	(Insertion) ~~Whenever the site is notified of a possible pregnancy, the patient should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female patient becomes pregnant, the patient must stop taking investigational product immediately and be withdrawn from the study~~…	8.4.1.3. **Pregnancy** **If a female patient becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 13.1.10 pregnancy is not considered an AE for reporting purposes. The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 13.1.10). New baseline procedures should include pregnancy testing**.	Was Section 8.4.1.1
8.4.2, Reasons for Mandatory Discontinuation of Investigational Product	8.4.2. ~~Other Reasons for Discontinuation of Investigational Product or Study Termination~~	8.4.2. Reasons for Mandatory Discontinuation of Investigational Product **Patients who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these patients should be encouraged to consent to the semiannual telephone contact and/or continued record review only to allow for secondary outcome events data to be collected.**	Now Section 8.4.3 and text added.
	~~8.4.2.3. Elevated Liver Enzymes~~	Section deleted.	Information in 8.4.1.2 now covers this.
8.4.3, Other Reasons for Discontinuation of Investigational Product or Study Termination	~~Subjects who discontinue investigational product are expected to continue in the study until the end of the study or at the discretion of the Sponsor. If a patient experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe.~~ ~~Early termination procedures should only be conducted if the patient withdraws consent (See Section 9.7.14).~~	8.4.3. **Other Reasons for Discontinuation of Investigational Product or Study Termination** The following events are considered appropriate reasons for **a patient to discontinue investigational product; however, these patients are expected to continue in the study until study termination (or at the discretion of the Sponsor):** • **Patient begins treatment with commercially available OCA.** • **The Investigator or Sponsor considers that it is advisable or in the best interest of the patient.**	Was Section 8.4.2 and additional text added.

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	~~It is agreed that, for reasonable cause, either the Investigator or the Sponsor, may terminate this study.~~ ~~The following events are considered appropriate reasons for a subject to discontinue from the study:~~	• **The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to study drug.** • **Withdrawal of consent** – **Consent may be fully withdrawn (in which case the patient discontinues both investigational product and study visits and procedures).** – **Consent may be modified to discontinue study visits but allow semi-annual telephone contact.** – **Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE) and liver-related clinical outcomes.** – **Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.12)**	
8.4.3.1. Withdrawal of Consent to Continue in the Study	8.4.3.1. Withdrawal of Consent … their consent to continue in the study at any time (Insertion) A reasonable effort must be made to…	**8.4.3.1. Withdrawal of Consent to Continue in the Study** **Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.12).**	Added more information regarding withdrawal from study.
8.4.3.2. Lost to Follow-Up	8.4.2.2. Lost to Follow-Up ~~If a patient fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the patient, he or she~~ will be ~~withdrawn from the study~~.	**8.4.3.2. Lost to Follow-Up** **Patients** will be **considered "lost to follow up" only after documented attempts to reach the patient prove unsuccessful.**	Updated text.
8.4.4, Patient Discontinuation Notification	8.4.~~3~~. Patient Discontinuation Notification The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the	8.4.**4**. Patient Discontinuation Notification The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s)	Clarified text.

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	primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. ~~Patients will be considered "lost to follow up" only after reasonable, documented attempts to reach the patient prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a patient fails to return for required study visits or discontinues from the study.~~ This information must be documented in the eCRF.	for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. This information must be documented in the eCRF.	
9.2, Concomitant Medications	~~Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section) during the study.~~ Concomitant medications will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). … taken ~~prior to (ie~~, within 30 days of Screening~~)~~ and … Concomitant medications should be stable prior to Day 1 ~~(ie no change in dosing within 3 months of screening).~~	Concomitant medications (**other than prohibited concomitant medications listed in Section 9.2.2**) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). … taken within 30 days of Screening and during the study must be recorded in the source documents and … Concomitant medications should be stable prior to Day 1.	Clarified use of concomitant meds**.**
9.2.1, Drug Interactions	~~Patients taking~~ bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be ~~instructed to stagger their dosing~~ of investigational product and UDCA, ~~ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (and UDCA;~~ ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration).	Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should **not** be **taken within 4 hours** of **taking investigational product (**and UDCA **if applicable),** ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration)**.**	Clarified use of concomitant meds.
9.2.2, Prohibited Medications	Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.~~2~~). ~~Fibric acid derivatives (fibrates) and other medication intended to lower blood triglyceride levels are also prohibited while on investigational product.)~~	Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.**3**).	Some patient may be expected to be on fibrates.
9.4.2, Blinding	The patients, Investigator, and study site staff will be blinded to…	The **Sponsor**, patients, Investigator, and study site staff will be blinded to…	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
9.6, Restrictions	Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited.	Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited. **Previous exposure to OCA (as a study participant or received commercial OCA therapy) is allowed within 3 months prior to enrollment in this study**	Updated to include patients who may be on prescribed OCA and who received investigational OCA as study participants.
9.7.1, Visit Procedures	(Insertion)	**Visit windows are specified in the Schedule of Study Procedures (Table 1).**	Added text pointing to visit windows for study procedures.
9.7.2, Informed Consent Procedures	…The patient must be willing and able to provide written informed consent (on hard copies ~~or on electronic devices such as iPads)~~ before entering the study.	The patient must be willing and able to provide written informed consent (on hard copies) before entering the study.	Updated language.
9.7.3, Assessing Cirrhosis	~~To determine which dosing regimen patients should follow, cirrhosis should be assessed by the Investigator at Screening Visit 1.~~ Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators: – varices ~~Patients will be dosed according to their CP Score calculated in the eCRF (see Section 14.1.1 and Table 12).~~ ~~Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in cirrhosis status will necessitate re-evaluation of the dosing regimen.~~	Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators: – **Gastroesophageal** varices	Clarified assessment instructions.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
9.7.4, Screening Procedures	Screening Procedures ~~(1 day to~~ 14 days prior to Day 1)	Screening Procedures (14 days **to 28 days** prior to Day 1)	Updated procedures to match updated protocol design.
	The Screening Visit assessments must be performed ~~within~~ ≤14 days prior to Day 1 to…	The Screening Visit assessments must be performed ≥14 days prior to Day 1 to…	
	The patient is to review and sign the ICF	• **Verify that the patient has fasted for at least 8 hours.** – **Record fasting status in the source and eCRF** – **If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits**	
	~~• Obtain blood samples for serum chemistry, hematology, and coagulation tests.~~		
	• Perform a physical examination.	Perform a physical examination, **including smoking and alcohol consumption history, and current habits for both.**	
	(Insertion)	• **Record the visit in IWRS**	
	• Perform TE using the Fibroscan® TE device. ~~If TE has been done within 3 months of Day 1 and a report/adequate data are available, a pretreatment TE at Day 1 is not required.~~ If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	• Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~• Provide kits and instructions for collection of stool specimens at home prior to the Day 1 visit~~	• Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required. If the ultrasound cannot be performed at Screening (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed anytime within the screening visit window or on Day 0. Results from the screening ultrasound should be reviewed to assess possible exclusion criteria prior to randomization.	Clarified sampling procedures.
9.7.5, Day 1 Procedures	☐ ~~Obtain blood samples for~~ markers of inflammation ☐ ~~ELF (including~~ HA, P3NP, and TIMP-1) ☐ ~~Trough~~ PK assessment	Markers of inflammation and fibrosis (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK -8-M30, HA, P3NP, and TIMP 1) **Fasting** PK assessment	Clarified sampling procedures
	…, after patient eligibility has been confirmed	… after patient eligibility has been confirmed. **Instruct the patient to take Day 1 dose on the day of this visit.**	Clarified procedures
	• Record the visit in IWRS and dispense investigational product ☐ Instruct the patient to begin dosing on the day. (Second to last bullet) …the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed.	• Record the visit in IWRS and dispense investigational product – Instruct the patient to begin dosing on the day **of the Day 1 visit.** …the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed. **Instruct the patient to take Day 1 dose on the day of this visit.**	Updated procedures to match updated protocol design.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
9.7.6, Week 3 Safety Visit Procedures	Week 3 ~~(~~Safety ~~Contact)~~	Week 3 Safety **Visit Procedures**	Updated procedures to match updated protocol design per PMR requirements.
	~~Patients should be contacted by telephone at Week 3 to assess for AEs and verify that s/he~~ is dosing as directed. • ~~Contact~~ patient ~~by phone/email~~.	**Preferably, the patient will come in to the clinic for this visit. Alternatively, the site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.** **Verify that patient** is dosing as directed. • **Verify that the** patient **has fasted for at least 8 hours.** □ **Record fasting status in the source and eCRF** • **If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.** • **Review and record prior concomitant medications.** • **Assess and record AEs.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess investigational product compliance, perform investigational product accountability**	
		• **Obtain blood samples for** □ **Serum chemistry, hematology, and coagulation** **Schedule the next visit, reiterate dosing instructions, and advise the patient:** **Week 6 visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 visit within the following Wednesday and Friday (Figure 2).** • □ **NOT to take investigational product on the morning of the next visit, and**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		☐ **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** ☐ **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.**	
9.7.8, Week 9 through Week 48 (Safety Contact)	(Insertion)	**Patients should be contacted by telephone/email at Week 9 and every 3 weeks afterward to Week 48.** • **Contact patient by phone/email.** • **Review and record prior concomitant medications.** • **Assess and record AEs.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess investigational product compliance, perform investigational product accountability.**	Section added to provide guidance for telephone/email safety contact.
9.7.9, Week 12, Week 24, Week 36 Procedures	Week 12 Procedures Obtain blood samples ~~for markers of inflammation~~ ☐ ~~ELF (including HA, P3NP, and TIMP-1)~~ ☐ C4, ~~and~~ FGF-19, ~~bile acids~~ ☐ ~~Trough~~ PK assessment	Week 12, **Week 24, Week 36** Procedures • **Assess investigational product compliance, perform investigational product accountability** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible. (Refer to Section 7.3)** • Obtain blood samples for ☐ **Serum chemistry, hematology, and coagulation** ☐ **Markers of Inflammation (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30)** ☐ **Bile Acid**/C4/FGF-19	Updated procedures to match updated protocol design.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		□ **Fasting** PK assessment • **Perform a urine-based β-hCG pregnancy test in females of childbearing potential.** • **Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit.**	
	• Serial PK assessment; the following procedures will be conducted in all patients	• Serial PK assessment at **Week 12 and 24 ONLY (not done at Week 36 and Week 42);** the following procedures will be conducted in all patients	Updated procedures to match updated protocol design.
9.7.9, Week 12, Week 24, Week 36 Procedures	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
	Insertion	• Perform an ultrasound for HCC surveillance at **Week 24 ONLY** (if equipment is unavailable, sites should make every attempt to use available community referral sites).	
	• ~~Assess the patient's supply of investigational product to ensure an adequate amount.~~	deleted	Deleted for clarity.
9.7.10 Week 18 and Week 30 Procedures		Added the following procedure: • **Dispense investigational product only if there is dose increase or as needed. No new IP bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each IP bottle before a new bottle will be dispensed.**	Section merged into 9.7.8, additional PK assessments added per

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~□~~ Obtain blood samples ~~for markers of inflammation~~ □ ~~ELF (including HA, P3NP, and TIMP-1)~~ □ C4, ~~and~~ FGF-19, ~~bile acids~~ □ ~~Trough~~ PK assessment Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose	• Obtain blood samples for – **Serum chemistry, hematology, and coagulation** – **Markers of inflammation and fibrosis (IL 6, hs-CRP, TNF α, IgM, IgG, IgA, CK 18 M30, ELF [HA, P3NP, and TIMP 1])** – **Fasting** PK assessment – **Bile Acid**/C4/FGF-19 • Serial PK assessment at **Week 12 and 24 ONLY (not done at Week 36)**; the following procedures will be conducted in all patients:□ Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 **7, 8, 9, and 24** hours post dose	PMR requirements.
	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume a **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
9.7.10, Week 24 Procedures	~~9.7.10, Week 24 Procedures~~	deleted	Incorporated into Section 9.7.8
9.7.11, Week 48 Procedures	9.7.1~~2~~	9.7.1**0, Week 48 Procedures**	Updated language.
	• Perform a physical examination,	• Perform a physical examination, **including smoking and alcohol consumption history, and current habits for both**	Clarify study procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	(Insertion)	• **Assess investigational product compliance, perform investigational product accountability.** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible (refer to Section 7.3)** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	Clarify study procedures.
	Obtain blood samples ~~for markers of inflammation~~ □ ~~ELF (including HA, P3NP, and TIMP-1)~~ □ C4, ~~and~~ FGF-19, ~~bile acids~~ □ ~~Trough~~ PK assessment	• **Perform urinalysis (dipstick)** • Obtain blood samples for – **Serum chemistry, hematology, and coagulation** – **Markers of inflammation and fibrosis (IL 6, hs-CRP, TNF α, IgM, IgG, IgA, CK 18 M30, ELF [HA, P3NP, and TIMP 1])** – **Fasting** PK assessment – **Bile Acid**/C4/FGF-19	Clarify study procedures.
	• Serial PK assessment; will ~~only~~ be conducted in patients ~~who are uptitrating to the next dose level.~~	• Serial PK assessment; **the following procedures** will be conducted in **all** patients.	Updated language.
		Immediately following 1 hr post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes)	Added more sampling times.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		□ Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, **7, 8, 9, and 24** hours post dose.	
	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
	Perform TE using the Fibroscan® TE device.	Perform TE using the Fibroscan® TE device. **If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.),** the **procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit**.	Clarified procedural instructions.
	• ~~Assess the patient's supply of investigational product to ensure an adequate amount.~~		Clarified procedural instructions
	• Schedule the ~~follow up~~ visit and advise the patient:	• Schedule the **next** visit**, reiterate dosing instructions**, and advise the patient: □ **NOT to take investigational product on the morning of the next visit, and** □ **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** □ **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted**.	Clarify study procedures.
9.7.12, Every 3 Months after Week 48	9.7.1~~3~~ Patients who have completed their 48-week double-blind treatment period will continue double blind treatment until all randomized patients have completed their ~~participation in the primary~~ treatment period and the database is locked…. and should not exceed the indicated maximal dose and frequency indicated for their CP category.	**9.7.11. Every 3 Months after Week 48** **Quarterly** • **Verify that the patient has fasted for at least 8 hours.** – **Record fasting status in the source and eCRF** – **If the patient reports having eaten within 8 hours, document accordingly in the source and**	Clarified dispensing instructions.

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	~~Patients will then have the option to continue into an open-label LTSE.~~	**eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.** • **Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess and record vital signs (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Perform assessments for calculation of CP Score (Section 14.1.1).** • **Administer Quality of Life and Patient questionnaires (see Section 13.2.6).** • **Assess investigational product compliance, perform investigational product accountability.** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible (refer to Section 7.3).**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		• **Perform urinalysis (dipstick)** • **Perform a urine-based β-hCG pregnancy test in females of childbearing potential.** • **Obtain blood samples for** – **Serum chemistry, hematology, and coagulation** • **Schedule the next visit, reiterate dosing instructions, and advise the patient:** – **NOT to take investigational product on the morning of the next visit, and** – **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** • **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.** **Patients will complete a TE/ELF (HA, P3NP and TIMP 1) and ultrasound (for HCC surveillance) assessment, every 6 months (±2 weeks) after Week 48.** **ECG will be done yearly (±2 weeks) after Week 48.**	
9.7.13, End of Study/Early Termination Procedures for Patients that Withdraw from Investigational Product or	9.1.14; End of ~~Treatment~~/Early Termination Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent … Patients who discontinue investigational product before are expected to continue … EOT/ET procedures will be required whenever patients discontinue treatment with investigational product	9.7.1**2**. . End of **Study**/Early Termination/**End of Treatment** Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent … Patients who discontinue investigational product **before Week 48** are expected to continue ... EOT (when subject discontinues investigational product)/ET procedures will be required whenever patients discontinue treatment with investigational product (**Table 1, Section 9.7.10**)	Clarified procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Withdraw Consent	When a patient discontinues investigational product ~~but~~ continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. (Insertion)	When a patient discontinues **or interrupts** investigational product **and** continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. **EOT and EOS visits are encouraged but at no time will a missed EOT or EOS visit be considered a protocol deviation.**	
9.7.13, Table 5, row 5	~~Treatment Interruption Interrupted RetainedRegular Visit Schedule Complete as close as possible to last dose of investigational product Complete at final study visit~~	Deleted	Removed to reduce confusion
10.3, Investigational Product Storage	~~Investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15ºC to 25ºC.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical studies are to be shipped and stored at 15°C to 25°C. Temperature excursions within the range of 2°C and 30°C for no more than a 6-month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20°C to 40°C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.**	Updated storage conditions per the Investigator's Brochure.
12, 12.1, Pharmacokinetic Blood Sampling	~~Subjects~~ with at least one PD assessment after dosing will be included in the combined PK/PD analyses Serial and ~~trough~~ PK assessments will be performed in all patients participating in the study. ~~At each visit~~, patients will provide…	**Patients in the PK Population** with at least one PD assessment after dosing will be included in the combined PK/PD analyses Serial and **fasting** PK assessments will be performed in all patients participating in the study. **At Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48**, patients will provide…	Specific dates are required to obtain optimum PK results

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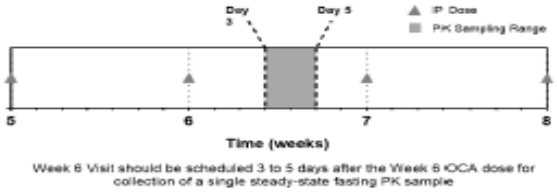
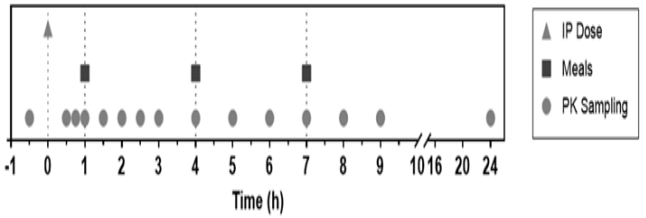
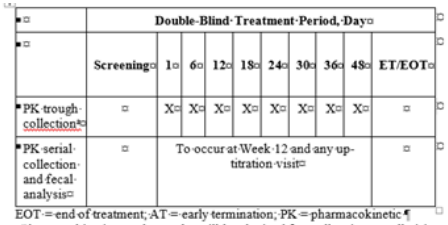
	(Insertion)	**Week 6 visit should occur 3, 4, or 5 days after the Week 6 dose, (eg if the Week 6 dose of drug is taken on a Sunday, the patient should come in for the Week 6 visit between Wednesday and Friday [Figure 2]).**	
	(Insertion) …serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose…	**Figure 2: Week 6 Sampling Schedule**  Week 6 Visit should be scheduled 3 to 5 days after the Week 6 OCA dose for collection of a single steady-state fasting PK sample **IP = investigational product; PK = pharmacokinetic** **At Weeks 12, 18, 24, 30, and 48,** Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5**,** 6, **7, 8, 9 and 24 hours postdose (Figure 3) for all patients. The patient will be given the option to return** to the **clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. The home health care agency must be advised one week in advance of the appointment.**	Added diagram and language to clarify PK sampling procedures.
	(Insertion)	**Figure 3: Pharmacokinetic Sampling Schedule**  At meal timepoints, meals are consumed immediately after the collection of the PK sample **OCA = obeticholic acid; PK = pharmacokinetic**	Added diagram and language to clarify PK sampling procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
12.1, Pharmacokinetic Blood Sampling	~~Table 7: Pharmacokinetic Sampling Schedule~~  Double Blind Treatment Period, Day Screening | 1 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | ET/EOT PK trough collection[a] | X | X | X | X | X | X | X | X PK serial collection and fecal analysis | To occur at Week 12 and any up-titration visit EOT = end of treatment; AT = early termination; PK = pharmacokinetic [a] Pharmacokinetic trough samples will be obtained from all patients at all visits prior to dose administration. [b] Serial PK assessments will be performed in all patients at Week 12. Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible and uptitrated their dose. Sample collection for fecal analysis will occur concurrent serial PK sampling visits only.		Replaced with other Figures 2 and 3.
	During the ~~double blind~~ treatment period and ~~double blind LTSE:~~ • Pharmacokinetic ~~trough~~ samples will be obtained from all patients at all visits prior to dose administration in accordance with ~~Table 7~~. • Serial PK assessments will be performed in all patients ~~at Week 12~~. ~~Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible~~ and ~~uptitrated their dose~~. ~~Sample collection for fecal analysis will occur concurrent with serial PK sampling visits only.~~	During the treatment period: • Pharmacokinetic **fasting** samples will be obtained from all patients at **Weeks 6, 12, 18, 24, 30, 36, and 48** prior to dose administration in accordance with **Figure 3**. • Serial PK assessments will be performed in all patients **at Weeks 12, 18, 24, 30, and 48.**	Clarify PK sampling and collection procedures.
12.2, Processing and Handling of Pharmacokinetic Samples	The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site and in a separate document before the study is initiated.	The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site **and home health care company** in a separate document before the study is initiated.	Added option of using home health care service.
13, Assessment of Safety	~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.~~ ~~Safety will be assessed in terms of AEs. All AEs, whether observed by the investigator, reported by the patient, noted from laboratory findings, or identified by other means, will be recorded from the time the patient signs his/her consent~~	deleted	Safety information updated to match Protocol 747-302.

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td></td><td>~~form (s)until the patient completes study participation (final Follow Up Visit).~~
~~Recording AEs/SAEs in the electronic data capture (EDC) system is the method for reporting AEs/SAEs. It is therefore imperative, that AEs/SAEs are recorded into the EDC.~~</td><td></td><td></td></tr>
<tr><td rowspan="2">13.1.1.3. Treatment-Emergent Adverse Event</td><td>13.1.1.~~2~~
~~A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.~~</td><td>Moved to Section 13.1.3. Recording Adverse Event Severity</td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>~~Table 9: Severity of Adverse Events~~
<table><tr><th>Grade</th><th>Clinical Description of Severity</th></tr><tr><td>~~1=Mild~~</td><td>~~Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.~~</td></tr><tr><td>~~2=Moderate~~</td><td>~~Minimal, local or noninvasive intervention indicated, or limiting age-appropriate instrumental activities of daily living.~~</td></tr><tr><td>~~3=Severe~~</td><td>~~Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.~~</td></tr></table></td><td>Table 9: Severity of Adverse Events
<table><tr><th>Grade</th><th>Clinical Description of Severity</th></tr><tr><td>1=Mild</td><td>Causing no limitation of usual activities; the patient may experience slight discomfort.</td></tr><tr><td>2=Moderate</td><td>Causing some limitation of usual activities; the patient may experience annoying discomfort.</td></tr><tr><td>3=Severe</td><td>Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.</td></tr></table></td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.3.1. Severity of Pruritus (as an Adverse Event)</td><td>~~To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used for AE reporting. As pruritus is a patientive symptom, clinical judgment should be used to determine its severity and management Table 10~~
Table 10 deleted.</td><td></td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.4.1. Reporting of Adverse Events</td><td>(Insertion)</td><td>…. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.</td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.4.2. Reporting of</td><td>~~• Telephone:~~ PPD
If an SAE is reported by ~~telephone or~~ fax, …</td><td>If an SAE is reported by fax, …</td><td>Number no longer in use.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Serious Adverse Events			
13.1.5.1. Potential Clinical Outcome Events	~~The events listed below will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events. These events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.~~ ~~Potential Clinical Outcome Events:~~ ~~Hospitalization for clinical complications of cirrhosis.~~ ~~Given that the Potential Clinical Outcome Events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously report suspected Potential Clinical Outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a "potential study event" on the Adverse Event eCRF and will be submitted for adjudication to the Adjudication Committee as described in Section 15.9.~~		Safety information updated to match Protocol 747-302.
13.1.7. Notification of Post-Treatment SAEs for Patients Who Continue in the Study	13.1.7. Notification of Post-~~Study~~ SAEs ~~If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2~~	13.1.7. Notification of Post-**Treatment** SAEs **for Patients Who Continue in the Study** **Post-treatment SAEs that occur in patients who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.** **SAEs that occur in patients who discontinue investigational product, initiate treatment with commercially available Ocaliva, and remain in the study must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2**.	Safety information updated to match Protocol 747-302. Deleted text is already in Section 13.1.8.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
13.1.8. Notification of Post--Study SAEs	(Insertion)	**13.1.8. Notification of Post-Study SAEs** **All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.**	Safety information updated to match Protocol 747-302.
13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	~~13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study~~ ~~Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2~~	Moved to 13.1.7	Safety information updated to match Protocol 747-302 9 (moved to 13.1.7).
13.1.10, Pregnancy and Follow-up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must ~~discontinue~~ investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing. ~~In the situation that the EDC is not functioning, the Medical Monitor should be notified by telephone. The investigator remains responsible for entering the pregnancy information into the EDC when the EDC becomes functional.~~	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must **interrupt treatment with** investigational product immediately (see Section) and the Sponsor must be notified within 24 hours of the Investigator's **awareness** of the pregnancy by completing the Pregnancy **CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to** PPD **or faxed to** PPD **The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.** **The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The patient must have a negative pregnancy test before restarting investigational product. If a patient's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy**	Safety information updated to match Protocol 747-302.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		confirmed by a serum β-hCG test before restarting investigational product.	
13.2.2, Physical Examination	13.2.~~1~~ (Insertion)	13.2.**2** A basic physical examination… **Smoking and alcohol consumption history and current habits will be recorded**….	Clarified assessments
13.2.5, Laboratory Assessments	~~For visits that require fasting~~, the Investigator or designee will verify that the patient has fasted for at least 8 hours …	**At all visits (except screening),** the Investigator or designee will verify that the patient has fasted for at least 8 hours…	Clarified visit procedures
	Blood samples for serum chemistry, coagulation, and hematology will be collected at ~~every visit~~…	Blood samples for serum chemistry, coagulation, and hematology and **urine samples** will be collected at **visits**…	Clarified what samples will be collected.
13.2.5, Laboratory Assessments, Table 9		Added the following labs: • Serum Chemistry – **CPK, TFT (TSH, free T3 and free T4)** • Urinalysis **(dipstick)** – **Pregnancy** • Noninvasive measurement… – **ELF (HA, P3NP, and TIMP-1), TE**	Updated lab tests to be performed.
	~~Biomarkers~~ of ~~Hepatic Fibrosis and/or~~ Inflammation; IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30, ~~and others as determined during course of study~~	Markers of Inflammation; IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30	Clarified assessments
	~~Genetics; -DNA including single nucleotide polymorphisms that may be involved in PBC; RNA~~	deleted	No longer doing this analysis.
13.2.5, Laboratory Assessments	(Insertion)	**PD markers**: C4, **FGF-19 and plasma bile acids**	Added new row

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td>13.2.5, Laboratory Assessments</td><td>(Insertion)</td><td>Laboratory reference ranges for the study will be based on the laboratory vendor range.</td><td>Added to satisfy PMR request.</td></tr>
<tr><td>14.1.1, Child-Pugh Score, Table 10</td><td><table>
<tr><th>Factor</th><th>Units</th><th colspan="3">Points</th></tr>
<tr><th></th><th></th><th>1</th><th>2</th><th>3</th></tr>
<tr><td><s>Serum bilirubin</s></td><td><s>µmol/L</s></td><td><s><35</s></td><td><s>35-50</s></td><td><s>>50</s></td></tr>
<tr><td><s>Serum albumin</s></td><td><s>g/L</s></td><td><s>>35</s></td><td><s>28-35</s></td><td><s><28</s></td></tr>
<tr><td>Hepatic encephalopathy</td><td></td><td><s>No</s></td><td></td><td></td></tr>
</table></td><td>Deletion

Encephalopathy now 0</td><td>Simplified CP scoring procedure.</td></tr>
<tr><td>14.2.1, Markers of Inflammation, Apoptosis and Necrosis</td><td>Blood samples for analytes including hs-CRP, IgM, TNF-α, and cytokeratin-18, neoepitope M30.</td><td>Blood samples for analytes including IL-6, hs-CRP, IgA, IgG, IgM, TNF-α, and cytokeratin-18, neoepitope M30.</td><td>Added additional markers.</td></tr>
<tr><td>15.4, Safety Analyses</td><td>No inferential comparison <s>of safety endpoints</s> will be performed. <s>All</s> safety <s>comparisons will be descriptive.</s></td><td>No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.</td><td>Clarified statistical analyses.</td></tr>
<tr><td>15.4.3, Adverse Events of Special Interest</td><td>… The <s>quartiles, including</s> the median <s>time-to-event</s> and <s>their respective</s> 2-sided 95% CIs, will be presented. <s>KM estimates will be plotted</s> as <s>a “survival curve” for each treatment group.</s></td><td>… The tabulation will include the KM estimate methodology using 25th, 50th (median), and 75th percentiles of the medians and corresponding with associated 2-sided 95% confidence intervals (CIs), if the medians can be estimated as well as percentage of censored observations.</td><td>Clarified statistical analyses.</td></tr>
<tr><td>15.5, Efficacy Analyses, 4th paragraph</td><td>… The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 95% CI of the difference will also be presented. <s>No formal hypothesis testing will be performed.</s></td><td>The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 2-sided 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 2-sided 95% CI of the difference will also be presented</td><td>Clarified statistical analyses.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
15.6, Additional Efficacy Analyses	The following clinical ~~outcomes~~ will be captured in the study: • All cause ~~mortality~~ • Liver related death • Liver transplant • Variceal bleed • Hepatic encephalopathy • Bacterial peritonitis • ~~Ascites~~ • ~~Hepatocellular carcinoma~~	The following clinical **endpoints** will be captured in the study : • **Time to death** (all-cause) • **Time to** liver-related death • **Time to hepatic failure** leading to liver transplant • **Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)** • **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:** – **Time to variceal bleed** – **Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)** – **Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)** • **Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).** The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-	Clarified statistical endpoints.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata. **In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC) will be summarized by treatment group using the same methods as defined above.**	
18.3, Written Informed Consent	(Insertion)	**The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the patient.**	Updated language.
21, List of References	(Insertion)	**Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014 Sep;61(3):642-59**. **Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007 Mar;45(3):797-805.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-72.**	Added new references
Appendix A, List of Study 747-401 Outcome Events	~~Some of the specified clinical endpoints will also by definition (see Section 13.1) qualify as Serious Adverse Events (SAEs). The sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 13.1.4). The Sponsor is responsible for regulatory reporting of SAEs including expeditious reporting of SAEs that are considered related to the investigational product and considered Unexpected by regulatory standards as defined in the Investigational Brochure.~~		This is covered in the main text.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~The Sponsor may consider the following lists of events to be exempt from expeditious regulatory reporting but will continue to report them in a non-expeditious manner:~~ ~~Potential Clinical Outcome Events:~~ ~~Liver-related events resulting in death~~ ~~Hepatic failure leading to liver transplant~~ ~~Variceal bleed~~ ~~Hepatic encephalopathy~~ ~~Spontaneous bacterial peritonitis~~ ~~Ascites~~ ~~Hepatocellular carcinoma~~		

APPENDIX B. SUMMARY OF CHANGES: PROTOCOL 747-401 VERSION 3 (DATED 04 JAN 2018)

Protocol 747-401 was revised to include the following information:

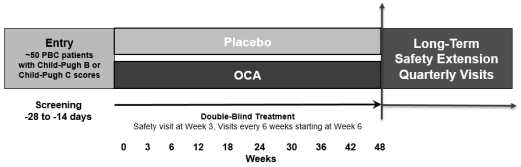
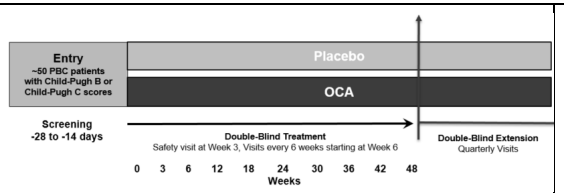
- The Introduction was revised to highlight the need for close monitoring specifically in patients with clinical evidence of hepatic decompensation and other complications due to advanced cirrhosis. Reference is made to sections describing specific criteria for investigational product adjustment, interruption, or discontinuation based on adverse events or laboratory values. This language also emphasizes the need for careful observation and evaluation of the entire clinical picture over and above system-generated alerts and flags for lab values.
- Dosing regimens were updated to modify dosing to one regimen for patients with moderate and severe hepatic impairment (eg, same for CP-B and CP-C), not to exceed 10 mg twice weekly, to align with label dosing guidelines. Titration is now only based on tolerability and not CP score.
- Reference to an option for open-label treatment was removed. An open-label extension will be considered only after review of blinded safety and PK data from the double-blind treatment period. For clarity, reference to the Long-Term Extension was changed to Double-Blind Extension; visits during this period remain the same.
- Protocol was updated with discontinuation criteria for decompensation events and biochemical thresholds. A plan for monitoring and drug-induced liver injury algorithm has been included to ensure careful monitoring and drug interruption/discontinuation. Analysis of decompensation events as adverse events of interest has been added. Additionally, “Close Observation” per FDA Guidance for Industry on Drug Induced Liver Injury” has been clearly defined in the protocol to ensure that patients who experience a potential DILI undergo a full evaluation.
- Guidance was added that patients should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as: pale-colored stools, urine color from pale to deep amber [dark], nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or the whites of eyes, and bruising easily.
- Guidance was added that the Investigator should contact the study Medical Monitor upon awareness when any signs and symptoms of hepatic decompensation are observed in any patient.
- Guidance was added for monitoring amylase and lipase levels in patients with suspected acute pancreatitis.
- Gallbladder assessments were added at Screening or Day 1.

Summary of Changes

The following revisions were made to the protocol in Protocol Version 3. Revised and new text in Version 3 is indicated in bold font, and the text deleted from Protocol Version 2 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Sponsor's Approval of the Protocol	PPD PhD Vice President, Clinical Development Intercept Pharmaceuticals, Inc.	PPD PhD **Sr** Vice President, Clinical Development Intercept Pharmaceuticals, Inc.	Signatory's title changed.
Study Personnel Contact Information	~~Medical Monitor~~ ~~Primary Contact:~~ PPD ~~MD~~ ~~Medical Director, Pharmacovigilance,~~ ~~Intercept Pharmaceuticals, Inc. (Intercept)~~ ~~Telephone:~~ PPD ~~Email:~~ PPD SAE Fax: PPD SAE Email: PPD	**Medical Monitor** **Primary Contact:** PPD **, DO, MSPH** **Senior Medical Director, Intercept Pharmaceuticals, Inc. (Intercept)** PPD **Secondary Contact:** PPD **MD** **Senior Medical Director, Intercept Pharmaceuticals, Inc. (Intercept)** PPD **24-Hour Telephone:** PPD SAE Fax: PPD SAE Email: PPD	Change in personnel.
Synopsis, Study Period; Section 7.1.3, Study Duration	Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). ~~Patients will then be given the option to go on open-label treatment.~~	Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). **An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.**	An open-label extension will only be considered only after review of blinded safety and PK data from the double-blind treatment period.
Synopsis, Phase of Development	Phase 4	Phase 4**: US, Canada, and the EU** **Phase 3b: All other regions**	Study is only considered a Phase 4 in regions where Ocaliva has received regulatory approval.

Synopsis, Additional Objectives; Section 6.3, Additional Objectives	Additional Objectives: • To evaluate the effect of OCA treatment compared to placebo on: ~~– Markers of inflammation~~ – Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score) – Noninvasive measurement of liver stiffness (transient elastography [TE])	Additional Objectives: • To evaluate the effect of OCA treatment compared to placebo on: – Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score) – Noninvasive measurement of liver stiffness (transient elastography [TE])	Samples were removed to simplify the study design.
Synopsis, Double-Blind Treatment Period; Section 7.1, Overall Study Design	Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. ~~At each visit (except screening and Week 3), fasting~~ PK assessments will be performed in all patients participating in the study~~.~~ Serial PK sampling will be performed at Week 12, 18, 24, 30, and 48. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. ~~Patients will then be given the option to go on open-label treatment.~~	Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. **Titration may be considered as early as the Week 12 Visit. Fasting** PK assessments will be performed in all patients participating in the study **on Day 1, Week 6, and Week 36.** Serial PK sampling **(which also includes a fasted PK assessment)** will be performed at Week 12, 18, 24, 30, and 48. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. **An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.**	Clarification for sites needed to clarify Fasted and Serial PK assessment timepoints. An open-label extension will only be considered only after review of blinded safety and PK data from the double-blind treatment period.

Synopsis, Study Design Diagram; Section 7.1.1 Study Design Diagram	 OCA = obeticholic acid, PBC = primary biliary cholangitis Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability ~~and CP score~~. Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.	 OCA = obeticholic acid, PBC = primary biliary cholangitis Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability. Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.	Clarification of extension period needed to ensure it is not confused with an open-label extension.

<table>
<tr>
<td>Synopsis, Dosing Regimen; Section 7.3 Planned Dosing Regimen</td>
<td>…
Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on ~~safety and~~ tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.
~~Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.~~
~~Patients with CP-C may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.~~
~~If, during the course of the study, a patient transitions from CP-B to CP-C, or vice versa, the maximal dose for the new CP classification would apply.~~
Planned OCA or Matching Placebo Dosing Regimen ~~by Child-Pugh Score~~
<table>
<tr><td></td><td colspan="2">Child-Pugh B (Moderate Hepatic Impairment)</td><td colspan="2">~~Child-Pugh C (Severe Hepatic Impairment)~~</td></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">~~Treatment Group~~</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>~~OCA~~</td><td>~~Placebo~~</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>~~5 mg once weekly~~</td><td>~~matching placebo~~</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo</td><td>~~5 mg twice weekly[b]~~</td><td>~~matching placebo~~</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo</td><td>~~10 mg twice weekly[b]~~</td><td>~~matching placebo~~</td></tr>
</table>
</td>
<td>…
Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.
Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.
Planned OCA or Matching Placebo Dosing Regimen
<table>
<tr><td></td><td colspan="2">Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)</td></tr>
<tr><td></td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo once weekly</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo twice weekly[b]</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo twice weekly[b]</td></tr>
</table>
[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.</td>
<td>Per FDA request to align dosing with label dosing guidelines for CP-B and CP-C patients.</td>
</tr>
</table>

	~~Titration 3[a]~~ | ~~5 mg once daily~~ | ~~matching placebo~~ | ~~NA~~ | ~~NA~~ [a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability ~~and/or changes in Child-Pugh Score at any time during the study.~~ [b] Dosing per the twice weekly schedule must be at least 3 days apart. ~~Over the course of the study, a patient's CP category may change. When a patient demonstrates a change in CP category, dosing should be reassessed and modified if appropriate. Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply. If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen should be followed.~~ ~~Maximum Dose for OCA or Matching Placebo for Changes in Child-Pugh Category~~ ~~Original Status | New Status[a]: Child-Pugh A | Child-Pugh B | Child-Pugh C~~ ~~Child-Pugh B | *No change* | *No change* | 10 mg twice weekly~~ ~~Child-Pugh C | 5 mg once daily | 5 mg once daily | *No change*~~ ~~[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for the planned dosing regimen.~~ ~~[b] Dosing per the twice weekly schedule must be at least 3 days apart.~~		
Synopsis, Key Inclusion Criteria; Section 8.2, Patient Inclusion Criteria	3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening ~~(ie, within 14 days before the first dose of investigational product):~~	3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening	Correction

<table>
<tr><td>Synopsis, Key Exclusion Criteria; Section 8.3, Patient Exclusion Criteria</td><td>4. ~~Hepatic~~ encephalopathy (as defined by a West Haven score of ≥2)</td><td>4. Current hepatic encephalopathy (as defined by a West Haven score of ≥2)</td><td>Correction</td></tr>
<tr><td>Synopsis, Key Exclusion Criteria</td><td>5. History or presence of other concomitant liver diseases including:
• Hepatitis C virus infection and RNA positive
• Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B antigen negative) may be included in this study after consultation with the medical monitor</td><td>5. History or presence of other concomitant liver diseases including:
• Hepatitis C virus infection and RNA positive
• Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the Medical Monitor</td><td>Correction</td></tr>
<tr><td>Synopsis, Duration of Treatment</td><td>Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). ~~Patients will then be given the option to go on open-label treatment.~~</td><td>Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.</td><td>An open-label extension will only be considered only after review of blinded safety and PK data from the double-blind treatment period.</td></tr>
<tr><td>Synopsis, Criteria for Evaluation; Section 11, Overview of Assessments, Table 7</td><td>
<table>
<tr><th>Secondary Objectives</th><th>Assessments</th></tr>
<tr><td>Changes in risk scores</td><td>Changes in MELD and in CP score and components of the CP score</td></tr>
<tr><td>Changes in liver biochemistry and hepatobiliary damage</td><td>Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets</td></tr>
<tr><td>PD parameters</td><td>FGF-19, C4, and plasma bile acids</td></tr>
<tr><th>Additional Objectives</th><th>Assessments</th></tr>
<tr><td>~~Markers of inflammation~~</td><td>~~IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30~~</td></tr>
<tr><td>Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis</td><td>TE and ELF (HA, P3NP, and TIMP-1)</td></tr>
</table>
</td><td>
<table>
<tr><th>Secondary Objectives</th><th>Assessments</th></tr>
<tr><td>Changes in risk scores</td><td>Changes in MELD and in CP scores and components of the CP score and MELD score</td></tr>
<tr><td>Changes in liver biochemistry and hepatobiliary damage</td><td>Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets</td></tr>
<tr><td>PD parameters</td><td>FGF-19, C4, and plasma bile acids</td></tr>
<tr><th>Additional Objectives</th><th>Assessments</th></tr>
<tr><td>Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis</td><td>TE and ELF (HA, P3NP, and TIMP-1)</td></tr>
</table>
</td><td>Risk score assessment clarified.

Markers of inflammation were removed to simplify the study design.</td></tr>
</table>

Section 14.1.1, Child-Pugh Score	<table><tr><th rowspan="2">Factor</th><th rowspan="2">Units</th><th colspan="3">Points</th></tr><tr><th>1</th><th>2</th><th>3</th></tr><tr><td rowspan="2">Serum bilirubin</td><td>µmol/L</td><td><3~~5~~</td><td>3~~5~~-50</td><td>>50</td></tr><tr><td>mg/dL</td><td><2.0</td><td>2.0-3.0</td><td>>3.0</td></tr></table>	<table><tr><th rowspan="2">Factor</th><th rowspan="2">Units</th><th colspan="3">Points</th></tr><tr><th>1</th><th>2</th><th>3</th></tr><tr><td rowspan="2">Serum bilirubin</td><td>µmol/L</td><td><3**4**</td><td>3**4**-50</td><td>>50</td></tr><tr><td>mg/dL</td><td><2.0</td><td>2.0-3.0</td><td>>3.0</td></tr></table>	Error correction
Synopsis, Safety Analyses; Section 15.4, Safety Analysis	Safety analyses will be conducted using the Safety population. Safety data, including AEs, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group.	Safety analyses will be conducted using the Safety population. Safety data, including AEs, **AEs of special interest including pruritus and hepatic safety**, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group.	Per FDA request
Synopsis, Additional Efficacy Analyses; Section 15.6, Additional Efficacy Analyses	Analyses of changes in liver stiffness and ELF~~, cytokeratin and TIMP-1, and markers of inflammation~~ will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.	Analyses of changes in liver stiffness **(TE)** and **liver fibrosis (**ELF [**HA, P3NP, and TIMP-1]),** will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.	Correction
Synopsis, Sample Size Justification; Section 15.2, Determination of Sample Size	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. ~~Ten~~ patients on placebo will be included as a comparator. An additional 20 patients ~~will~~ be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. **A total of 30 patients is adequate with 10** patients on placebo **to** be included as a comparator **and 20 patients on OCA**. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized **in a 1:1 ratio to 1 of the 2 treatment groups: Placebo and OCA.**	Clarification.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 5.1, Overview of Disease State and OCA	In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication~~.~~	In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication**, and in May 2017 Ocaliva received approval from Health Canada. Study 747-401 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC (ie, in the US, Canada, and the EU). In all other regions, this study is considered Phase 3b.**	Ocaliva has been approved in Canada since last version of protocol. Study is only considered a Phase 4 in regions where Ocaliva has received regulatory approval.
Section 5.3, Clinical Development of Obeticholic Acid	As of ~~31 Jan~~ 2017, approximately ~~2186 patients~~ have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~525~~ patients had PBC, ~~686~~ patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, ~~52~~ patients had primary sclerosing cholangitis (PSC), and ~~5~~ patients had biliary atresia.	As of **13 Oct** 2017, approximately **2690 subjects** have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **552** patients had PBC, **1141** patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, **73** patients had primary sclerosing cholangitis (PSC), and **6** patients had biliary atresia.	Updated exposure numbers available

5.4.2, Rationale for Obeticholic Acid Dose and Duration	Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3). ~~The dosing regimen in this study follows the FDA-approved prescribing information, with the exception of the maximum allowed dose in patients with moderate impairment. While the prescribing information allows for a maximum dose of 10 mg twice weekly for patients with moderate impairment, the protocol allows for a maximum dose of 5 mg once daily. The choice of 5 mg once daily is supported by the estimated steady-state liver and plasma exposure of total OCA for patients with moderate hepatic impairment receiving a 5 mg once daily dose relative to healthy patients receiving a 10 mg dose. A maximum allowed dose of 5 mg once daily in patients with moderate hepatic impairment is estimated to achieve liver exposure similar to non-hepatically impaired patients receiving a 10 mg daily dose and maximize efficacy in this patient population.~~	Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).	Text no longer applicable since all dosing regimens will follow FDA-approved prescribing information.

Section 5.5, Importance of Monitoring Disease Progression	New Section	**Given PBC is a chronic, progressive liver disease, it is important that patients with PBC are closely monitored to ensure early identification of decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve patient oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual patients to determine on an ongoing basis the totality of a patient's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring.** **Patients will be monitored for potential hepatic injury and/or decompensation. Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 8.4 and Section 7.6. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.**	Language added to generate Investigator awareness of the disease progression trajectory and unpredictable nature of progression in patients at high risk, as well as incorporation of language regarding altered bile acid and OCA PK and drug exposure in patients with hepatic impairment and the need for close vigilance to identify potential liver toxicity or decompensation.

Section 5.6, Summary of Known Potential Risks with Investigational Product	~~The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy patients, but with a much lower frequency than that observed in patients with PBC.~~ ~~Consistent with the dose-limiting hepatic toxicities observed in the non-clinical studies and the chemical characteristics of OCA as a bile acid and detergent, dose-related but reversible and asymptomatic increases in ALT and AST were observed in healthy volunteers treated with multiple doses of OCA starting at the 100 mg dose (Study 747-102).~~ ~~In patients with chronic liver disease such as PBC, hepatobiliary findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed. These findings were seen more frequently with doses of OCA 10 mg once daily to OCA 50 mg once daily (up to 5x the highest recommended dose). In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.~~ ~~Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDLc) and an increase in low density lipoprotein (LDLc). Notably, in patients with PBC, the decrease in mean HDLc levels occurred early and stabilized within 3 months after which time levels generally remained constant over the course of treatment. The average levels of HDLc remained within normal limits. Commensurate with decreases in HDLc, decreases in total cholesterol were observed in patients with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA treated patients with the exception of a modest transient and early rise after initiation of treatment.~~ ~~Based on previous PK and short-term studies in patients with hepatic impairment, increased systemic exposure was not associated with an apparent change in the safety profile of OCA as assessed by the incidence and severity of AEs or by changes in clinical laboratory tests. Hepatotoxicity has been associated with increased liver concentrations of OCA. Hepatic impairment does not~~	**The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk.** **<u>Clinical Data</u>** **In two Phase 2 studies and a Phase 3 study evaluating OCA in the treatment of subjects with PBC, hepatic adverse events were observed in subjects receiving doses of OCA ranging from the maximum approved dose of 10 mg once daily to 50 mg (5 times the highest recommended dose).** **Recent safety findings in NASH clinical trials include 2 cases of hepatic decompensation reported as SUSARs, 1 of which resulted in death. Both cases involved numerous confounding factors that make evaluation of association with treatment difficult. Details for both events are provided in the Investigator's Brochure Addendum 1 to Version Number: 16 (31 March 2017), Effective Date: 02 October 2017.** **The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease.** **Changes in lipid profiles have also been observed with OCA dosing, including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further.** **Independent data monitoring committees (DMCs) have performed detailed reviews of several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by**	Updated in relations to other revisions made per FDA request.

	~~affect the ability of OCA to activate FXR in the intestine and the liver.~~ Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.		**treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification.** **Post-Marketing Cases in PBC** **As of September 2017, greater than 3000 patients have received Ocaliva® in the post-marketing setting. In patients with moderate to severe hepatic impairment (Child-Pugh B and C), liver decompensation, liver failure, and death have been reported when Ocaliva was dosed up to 7 times the recommended once weekly starting dose for such patients. Based on the initial medical assessment of these cases, which included patients having undergone liver transplant, there was insufficient evidence suggesting a causal relationship between higher than recommended dosing and the reported adverse events. However, Intercept Pharmaceuticals, Inc. (the Sponsor) continues to assess the potential association between adverse events, including deaths, and the higher than recommended dosing of Ocaliva observed in PBC patients with moderate to severe hepatic impairment (Child-Pugh B and C) through ongoing post-marketing pharmacovigilance activities.** **Signs and symptoms reported in patients experiencing liver-related adverse events who received Ocaliva include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice, and liver decompensation.** Refer to the IB for additional information regarding the known potential risks with the investigational product.	
Section 7.1.2, Schedule of Study Procedures, Table 1	Treatment Period (Weeks)	~~Long-Term Safety~~ Extension	**Double-Blind** Treatment Period (Weeks)[b]	**Double-Blind** Extension	Clarification

Section 7.1.2, Schedule of Study Procedures, Table 1	Insertion	**Week 42 Visit added with assessments to match Week 3 Visit plus assesments to assess for dose titration and dispense IP.**	Correction
Section 7.1.2, Schedule of Study Procedures, Table 1, Screening, Day 1	Insertion	**Gallbladder assessment (ultrasound)**	Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications).
	Insertion	Footnotes added r **If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required.** **s If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.**	
Section 7.1.2, Schedule of Study Procedures, Table 1	~~Markers of Inflammation: IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30~~	Deletion	Samples were removed to simplify the study design.
Section 7.1.2, Schedule of Study Procedures, Table 1	Insertion	**Amylase and Lipase: Sample to be collected if the patient experiences acute pancreatitis or cholecystitis.**	Per FDA request.
Section 7.1.2, Schedule of Study Procedures, Table 1	PK Fasting Collection *Removed for Weeks 12, 18, 24, 30, and 48/ET/EOS/EOT*	Deletion	Clarification for sites needed to clarify Fasted and Serial PK assessment timepoints. Serial PK is fasted, so indicating both types of assessments for these days was redundant.
Section 7.1.2, Schedule of Study Procedures, Table 1	Insertion	Footnote added to Serum Chemistry/Hematology/Coagulation l **MELD values will be calculated based on serum chemistry coagulation values at each visit.**	Clarification.
Section 7.4, Monitoring and Management of Potential Hepatic Injury and/or Disease Progression	New Section	**Given the chronic nature of PBC, it is important to monitor for potential hepatic injury, disease progression and/or hepatic decompensation. Child-Pugh and MELD scores will be reviewed at each visit where labs are drawn (Table 1). In addition, adverse events, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.2. Based on biochemical and clinical assessments, the investigational product**	Extensive safety monitoring and dosing adjustments, interruptions, or discontinuations are required given the elevated risk of decompensation and higher hepatic exposure to OCA in this population. It is important that Investigators construct an entire clinical picture, which includes

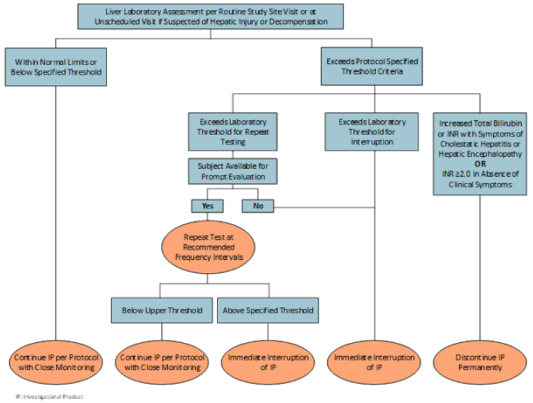
		may be interrupted or discontinued per criteria discussed in Section 7.4.2 and Section 7.4.3, and close monitoring procedures will be implemented (refer to Section 7.6).	not only rules based monitoring but careful evaluation of signs and symptoms of potential decompensation and diagnostic dilemmas.
Section 7.4.1, Signs and Symptoms of Potential Hepatic Injury or Decompensation	New Section	**Patients should be instructed to contact study personnel if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting** **<u>Signs and Symptoms of Hepatic Injury or Decompensation:</u>** • **Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark] (reflecting impaired bilirubin metabolism)** • **More general signs and symptoms of ascites and encephalopathy: confusion, swelling of the legs or abdomen** • **Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite** • **Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea for more than 4 days) and should be an indication for prompt investigational product interruption and complete patient evaluation** **<u>Other Symptoms:</u>**	Per FDA request.

		• **Worsening of renal function or likely dehydration** **<u>Healthcare Provider (HCP) Interactions:</u>** • **Visits to primary HCP or referral to any specialist for any new symptoms (other than ongoing care for stable comorbidities)** • **New medications or changes to current medications prescribed from HCP or any new over the counter medications or herbal supplements** • **Laboratory procedures or assessments performed by an HCP** **Signs and symptoms for potential hepatic injury or decompensation should be followed by (1) evaluation of liver biochemistry for suspected drug-induced liver injury (DILI) or potential hepatic decompensation (Section 7.4.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.4.3), (3) triggering of close monitoring or investigational product interruption/discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 13.1), and (5) contact with the Medical Monitor.**	
Section 7.4.2, Liver Biochemistry Assessments for Potential Hepatic Injury or Hepatic Decompensation	New Section	**Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of patients for potential hepatic injury or hepatic decompensation. These assessments will be performed at:** • **Each protocol-specified visit (Table 1)** • **Unscheduled visits as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered** **It is important that the laboratory assessments be completed as required and that the central**	Per FDA request.

laboratory be used for assessments whenever possible. In the event that a patient cannot return to the clinic for a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local lab is permissible at the discretion of the Investigator. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges.

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and, potentially, a complete patient evaluation (depending on the repeat result) are summarized in Table 3.

Figure 2: DILI Management Algorithm



DILI = drug-induced liver injury; IP = Investigational Product

NOTE Other laboratory criteria include: ALT, AST, total bilirubin, INR, and electrolytes (sodium).

Table 3 Liver Laboratory Criteria for Monitoring of Suspected Hepatic Injury or Potential Hepatic Decompensation and Criteria for Interruption or Discontinuation of Investigational Product

		It should be noted that it is difficult to recognize every potential marker of hepatic or renal deterioration. There is no substitute for good medical judgment. Investigators will be reminded to be cautious and mindful in their evaluation of patients' symptoms, signs, and laboratory results. However, for example, a single abnormal laboratory analyte result may be artefactual; accordingly, Investigators will be allowed to implement an alternate follow-up procedure if considered appropriate based on their medical judgement, but only after documented agreement with the Sponsor's Medical Monitor.	
7.4.3, Clinical Criteria for Monitoring for Potential Hepatic Decompensation	New Section	**Patients will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 4.** **Investigational product should be discontinued permanently if the patient received a liver transplant or experiences multi-organ failure as defined in Table 4, Part A. Patients should continue to return for scheduled study visits for safety follow up.** **Patients who experience other potential hepatic decompensation events defined in Table 4, Part B should be closely monitored until normalization or stabilization. Patients may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.** **Table 4 Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Interruption / Discontinuation of Investigational Product**	Per FDA request.
7.5, Dose Titration Criteria	Dose ~~Adjustment~~ Criteria Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns ~~or as a result of changes in a patient's CP Score~~. Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as	Dose **Titration** Criteria Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns. Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as assessed by a review of AEs and safety laboratory	Updates made to reflect titration for dosing per label dosing guidelines.

	assessed by a review of AEs and safety laboratory results). In general, down-titration may be done in response to tolerability concerns and can occur at any time. Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated ~~for each dosing regimen~~ as defined in Section 7.3. **Scheduled Dose Titration -** After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose ~~or dosing frequency~~ for patients may occur no earlier than 6 weeks following an up-titration. **Tolerability Dose Titration -** Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability) ~~**Dose Titration due to Change in CP Score** Over the course of the study, a patient's CP category may change. When a patient demonstrates a change in CP category (as assessed per Table 12), dosing should be reassessed and modified if appropriate (Table 2). Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply (Table 2). If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen (Table 2) should be followed.~~ ~~Table 3: Maximum Daily dose based on change in Child-Pugh Category~~	results). In general, down-titration may be done in response to tolerability concerns and can occur at any time. Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated as defined in Section 7.3. Scheduled Dose Titration - After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose for patients may occur no earlier than 6 weeks following an up-titration. Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability).	

	~~Original Status~~ / ~~New Status[a]~~: ~~Child-Pugh A~~ | ~~Child-Pugh B~~ | ~~Child-Pugh C~~ ~~Child-Pugh B~~: ~~*No change*~~ | ~~*No change*~~ | ~~10 mg twice weekly~~ ~~Child-Pugh C~~: ~~5 mg once daily~~ | ~~5 mg once daily~~ | ~~*No change*~~ ~~[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.3 .~~ ~~[b] Dosing per the twice weekly schedule must be at least 3 days apart.~~ ~~CP Scores will be calculated at all study visits (except Week 3). While PBC-specific versions of CP scores are available, this study will use the standard calculation (Pugh 1973, Lucey 1997). All associated visit data (including central laboratory results) should be entered into the electronic case report form (eCRF) in a timely fashion to confirm that the patient's CP Score has not changed. If a change in CP Score is observed independent of a study visit, the patient should be contacted via phone to discuss the need for a dosing modification and should be asked to return to the investigative site as soon as possible if a new bottle of investigational product is required to be dispensed.~~		
Section 7.6, Close Observation	New Section	**If investigational product is interrupted or discontinued as described in Section 8.4, patients should be closely monitored (contacted by the site a minimum of every 2 weeks and scheduled visits every 6 weeks; if returning to the site for a scheduled visit is not feasible, use of a local lab may be permissible at the Investigator's discretion). At a minimum, the following assessments should be conducted at each study visit:** • **Physical exam and thorough review of patient reported signs and symptoms,** • **Liver biochemistry (including ALP, ALT, AST, GGT, total and conjugated bilirubin, creatinine, and**	Per FDA request.

		albumin), prothrombin time (PT)/INR, serum electrolytes, and assessment of Child Pugh (only if the patient is at the study site) and MELD scores. **In addition, a trough pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any patient who develops an AE that is indicative of or consistent with hepatic injury or decompensation.** **The following additional monitoring procedures should be performed for events of potential hepatic injury (per FDA Guidance for Industry on Drug Induced Liver Injury) or suspected hepatic decompensation based on criteria described in Section 7.4.1, Section 7.4.2, Section 7.4.3. These cases need to be discussed with the Sponsor's Medical Monitor:** • **Repeating liver biochemistry and function tests as described in Section 7.4.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic, as clinically indicated.** • **Obtaining a more detailed history of symptoms and prior or concurrent diseases.** • **Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs potentially hepatotoxic,**	

		continued use of investigational product should be discussed with the Sponsor's Medical Monitor. The patient may be discontinued from investigational product, if clinically appropriate. • **Obtaining a history of exposure to environmental chemical agents or herbal supplements which may be associated with liver toxicity.** • **Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute HBV infection), and E; autoimmune or alcoholic hepatitis; Wilson's disease, hypoxic/ischemic hepatopathy; and biliary tract disease.** • **Investigators should consider testing for Hepatitis E virus when assessing for hepatic decompensation as infection with Hepatitis E virus in patients with chronic liver diseases such as PBC may rapidly worsen with signs and symptoms similar to drug induce liver injury (Kumar 2013)** • **Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).** • **Seeking hepatology consultation, if the Investigator is not a hepatologist**	
Section 8.4, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	Investigational product may be temporarily decreased (eg, ~~by decreasing dosing frequency~~) or temporarily or permanently stopped based on tolerability concerns. ~~The dose~~ of investigational product should be ~~resumed to the maintenance dose in a blinded manner once the issues relating to the lack of~~ tolerability ~~are resolved~~. ~~Patients who are discontinued from~~ investigational product ~~prior to completion of the study are encouraged~~	Investigational product may be temporarily decreased (eg, **from 10 mg twice weekly to 5 mg twice weekly, or from 5 mg twice weekly to 5 mg once weekly**) or temporarily or permanently stopped based on tolerability concerns. **Investigational product may be resumed at the maintenance dose upon resolution** of **gastroenteritis or worsening renal function or dehydration if there is no evidence of liver injury.**	Per FDA request.

	~~to~~ continue to follow the regular visit schedule, with the exception of PK sampling, but may withdraw consent at any time.	**For rechallenge following all other dose interruptions (see Table 5),** investigational product should be **initiated at a lower dose and patients monitored more frequently with up-titration considered based on** tolerability. **Adjustments, interruptions, discontinuation, and any rechallenge of** investigational product **should be implemented per the criteria outlined in Table 5. Patients that discontinue investigational product are expected** to continue **in the study (and** follow the regular visit schedule, with the exception of PK sampling **[trough PK may be required in the event of an AE consistent with hepatic injury or decompensation]) until the end of the study**, but may withdraw consent at any time. **Table 5 Criteria for Dose Adjustment, Interruption, Discontinuation, and Rechallenge**	
8.4.1, Reasons for Additional Monitoring of Mandatory Interruption of Investigational Product; 8.4.1.1, Reasons for Additional Monitoring Related to Liver Chemistries; 8.4.1.2, Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries; 8.4.1.3, Pregnancy; 8.4.2., Reasons for Mandatory Discontinuation of Investigational Product	~~8.4.1. Reasons for Additional Monitoring or Mandatory Interruption of Investigational Product~~ ~~8.4.1.1. Reasons for Additional Monitoring Related to Liver Chemistries~~ ~~Patients who develop ALT or AST >2× baseline (and >ULN) or total bilirubin >1.5× baseline (and >ULN) should have repeat testing within 48 to 72 hours to confirm values. Patients with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or INR with persistent increases in ALT or AST should also be closely monitored.~~ ~~8.4.1.2. Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries~~ ~~Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:~~ ~~• AST and/or ALT >3× baseline (and >ULN)~~ ~~• Total bilirubin >2× baseline (and >ULN)~~ ~~Repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing should be performed. Detailed adverse event information should also be collected, and the patient should be investigated for possible causes of the liver~~	Deletion	Replaced by text in in other sections added per FDA request.

	~~chemistry changes, as appropriate. The Investigator should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable.~~ ~~If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), patients should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms.~~ ~~For the purposes of this protocol, if the above referenced significant elevation in liver enzyme or bilirubin levels resolve following interruption of investigational product and no other cause for the elevation is identified, the elevations should be assumed to be related to investigational product and investigational product should be discontinued. If the liver enzyme or bilirubin levels do not resolve following interruption of investigational product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the patient may be re-challenged following a discussion between the Investigator or designee and the Sponsor.~~ ~~Elevation of liver enzymes or bilirubin is based on comparison to baseline values defined as the mean of all available Screening and Day 1 values, which are the mean of all available evaluations prior to the first administration of investigational product. At least 2 of these samples will be obtained a minimum of 2 weeks apart during the Screening period. Elevations that occur gradually over the course of the study may be indicative of disease progression and should be assessed as clinically appropriate. Liver enzyme and bilirubin elevations that occur over a shorter time, such as within a 6-month period, should be evaluated for drug-induced liver injury as provided in the guidelines below.~~ ~~If at any time a patient develops signs or symptoms of hepatotoxicity such as new-onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>7%) in combination with elevations in liver enzymes, investigational product~~		

	~~should be interrupted and liver enzymes monitored until signs or symptoms resolve.~~ ~~Patients who develop evidence of severe drug-induced liver injury that is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged. Severe drug-induced liver injury includes, but is not limited to, functional hepatic impairment, as indicated by rising bilirubin or INR that cannot be explained by progression of disease. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.~~ ~~If after all investigations and actions outlined above have been completed, the investigator determines that the elevations in liver biochemistries are considered not related to investigational product, the Sponsor must be contacted before investigational product can be reinitiated. Follow-up procedures for patients resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment. Results must be reported to the site as soon as possible so the Investigator can determine if it is appropriate for the patient to continue treatment.~~ ~~The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.~~ ~~All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 15.9).~~ ~~8.4.1.3. Pregnancy~~ ~~If a female patient becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 13.1.9 pregnancy is not considered an AE for reporting purposes. The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 13.1.9). New baseline procedures should include pregnancy testing.~~		

	~~8.4.2. Reasons for Mandatory Discontinuation of Investigational Product~~ ~~Patients who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these patients should be encouraged to consent to the semiannual telephone contact and/or continued record review only to allow for secondary outcome events data to be collected.~~		
Section	**Original Text (Version 2)**	**Revised Text (Version 3)**	**Key Change** **Reasons / Justification for Change**
Section 9.5.2., Patient Numbers	~~Patients will be identified by a~~ unique ~~6-digit number,~~ independent of the randomization number. The first 3 digits ~~will~~ represent the site number and the last ~~three~~ digits ~~will~~ represent ~~the Screening~~ number.	**Patients are assigned using a** unique **10-character identifier (AAA-BBBCCC),** independent of the randomization number. The first 3 digits **represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits** represent the site number **(BBB). The** last **3** digits represent **a unique screening** number **that is assigned in sequential order at each site starting with 001 (CCC).**	Update per current practice.
Section 9.7.2, Informed Consent Procedures	The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated consent form. ~~Patients will also be provided a separate ICF before providing blood samples for genetic analysis and must be willing and able to provide consent as described above.~~	The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated **informed** consent form **(ICF)**.	Correction. There is no separate ICF for this study.

Section 9.7.4, Screening Procedures (14 Days to 28 Days prior to Day 1)	Insertion	• Perform an ultrasound for HCC surveillance and **evaluation of gallbladder status** (if equipment is unavailable, sites should make every attempt to use available community referral sites). If…	Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications).
Section 9.7.5, Day 1 Procedures (Randomization)	• Obtain blood samples for o Serum chemistry, hematology, and coagulation o Markers of ~~inflammation and~~ fibrosis (~~IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30,~~ ELF [HA, P3NP, and TIMP 1]) o Fasting PK assessment o Bile Acid/C4/FGF-19 • Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	… • Obtain blood samples for o Serum chemistry, hematology, and coagulation o Markers of fibrosis (ELF [HA, P3NP, and TIMP 1]) o Fasting PK assessment o Bile Acid/C4/FGF-19 • Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit. • **If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.**	Markers of inflammation were removed to simplify the study design. Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications).

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 9.7.5, Day 1 Procedures (Randomization); Section 9.7.11, Week 48 Procedures; 9.7.12, Every 3 Months after Week 48	• Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s)~~; s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and~~ – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	• Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s) **to the visit** – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	Correction. Patients will only be dosed in the clinic on visits with Serial PK.
Section 9.7.6, Week 3 **and Week 42** Safety Visit Procedures	Insertions.	Week 3 **and Week 42** Safety Visit Procedures … • Assess investigational product compliance, perform investigational product accountability. • **For Week 42 Only: Assess for dose titration, if eligible. (Refer to Section 7.3)** • **For Week 42 Only: Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed** • Obtain blood samples for - Serum chemistry, hematology, and coagulation • Schedule the next visit (Week 6 **or Week 48**), reiterate dosing instructions, and advise the patient: **For Week 3 Only:** - Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken	Correction to add Week 42 visit. Additional clarifications needed to distinguish certain assessments from Week 3. Clarification on which visits will have in-clinic dosing.

		on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3). **- NOT to take investigational product on the morning of the next visit, and** **- To bring the investigational product bottle(s) to the visit** **- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.** **For Week 42 Only:** - NOT to take investigational product on the morning of the next visit, and - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	
Section 9.7.7, Week 6 Procedures	Insertion	**Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3).**	Clarification.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 9.7.9, Week 12, Week 24, Week 36 Procedures	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of ~~inflammation and~~ fibrosis (~~IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30,~~ ELF [HA, P3NP, and TIMP 1]) – Bile Acid/C4/FGF-19 – Fasting PK assessment … • Serial PK assessment at Week 12 and 24 ONLY (not done at Week 36~~ and Week 42~~); the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of fibrosis (ELF [HA, P3NP, and TIMP 1]) – Bile Acid/C4/FGF-19 – Fasting PK assessment (**Week 36 only**) … • Serial PK assessment at Week 12 and 24 ONLY (not done at Week 36); the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)	Markers of inflammation were removed to simplify the study design. Clarification of serial and fasting PK assessments. Clarification of water and meal restrictions on visit day. Clarification of which visits have in-clinic dosing.

	– Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose Note: Patients should only consume a meal following the 4-hour and 7-ho~~ur PK assessment times (see Figure 4). Patients should not drink any water until at least one hour postdose.~~ • Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	– Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose Note: Patients should **not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.** • Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s) **to visits**; s/he will dose at the clinic **for Week 18 and Week 30 visits** (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	
Section 9.7.10, Week 18 and Week 30 Procedures	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Bile Acid/C4/FGF-19 ~~– Fasting PK assessment~~ …	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Bile Acid/C4/FGF-19 …	Fasting PK removed; serial PK on this visit is fasted. Clarification of water and meal restrictions on visit day Clarification on which visits will have in-clinic dosing.

	• Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose ~~Note: Patients should only consume a meal following the 4-hour and 7-hour PK assessment times (see Figure 4). Patients should not drink any water until at least one hour postdose.~~ • Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is	• Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose **Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.** • Schedule the next visit, reiterate dosing instructions, and advise the patient:	

	required prior to all study visits, but water is permitted.	– NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s) **to both visits**; s/he will dose at the clinic **on Week 24** (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	
9.7.11, Week 48 Procedures	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of ~~inflammation and~~ fibrosis (~~IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30,~~ ELF [HA, P3NP, and TIMP 1]) ~~– Fasting PK assessment~~ – Bile Acids/C4/FGF-19 • Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of fibrosis (ELF [HA, P3NP, and TIMP 1]) – Bile Acids/C4/FGF-19 • Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. – Collect blood samples at: 30 min, 45 min, 1 hour postdose	Markers of inflammation were removed to simplify the study design. Fasting PK removed; serial PK on this visit is fasted. Clarification of water and meal restrictions on visit day

	arrival for this visit) with 240 mL (8 oz.) of water. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose ~~Note: Patients should only consume meal following the 4-hour and 7-hour PK assessment times (see Figure 4). Patients should not drink any water until at least one hour post dose~~	– Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose **Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.**	
Section 12.1, Pharmacokinetic Blood Sampling	… Week 6 Visit should occur 3, 4, or 5 days after the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure ~~2~~]). … Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be provided following collection of the 1-, 4-, and 7-hour PK sample~~; the meal will be a meal~~	… Week 6 Visit should occur 3, 4, or 5 days after the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure **3**]). … **During the treatment period:** • **Pharmacokinetic fasting samples will be obtained from all patients at Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48**	Clarifications.

	~~replacement drink with nutrition~~ information ~~that has been~~ submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the ~~7~~-hour sample collection. ~~During the treatment period:~~ ~~• Pharmacokinetic fasting samples will be obtained from all patients at Weeks 6, 12, 18, 24, 30, 36, and 48 prior to dose administration in accordance with Figure 3.~~ ~~• Serial PK assessments will be performed in all patients at Weeks 12, 18, 24, 30, and 48.~~	**prior to dose administration in accordance with Figure 4.** • **Serial PK assessments will be performe in all patients at Weeks 12, 18, 24, 30, and 48.** Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal **replacement drink** will be provided following collection of the 1-, 4-, and 7-hour PK sample. **The nutritional** information **of the meal replacement drink should be** submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the **9-**hour sample collection.	
Section 13.1.1.1, Adverse Event	Insertion	**Patients should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as: pale-colored stools, urine color from pale to deep amber [dark], nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or the whites of eyes, and bruising easily.**	Given this is an at risk population, patients should be reminded to contact the Investigator or study coordinator in case they experience side effects or any other medical concerns and be aware of the signs and symptoms of potential hepatic decompensation.
Section 13.1.1.4, Adverse Events of Special Interest	Insertion	**The following decompensation events are adverse events of special interest; a subset of these are also captured as additional efficacy assessments (see Section 14.2.3).** • **Variceal bleeding or recurrent variceal bleeding documented by endoscopy OR patient presenting with anemia or melena (hemoglobin drop ≥2 gm/dL) and found to have varices documented by endoscopy,**	Per FDA request.

		irrespective of hospitalization or requirement of blood transfusion. • **Gastrointestinal bleeding as a result of gastric or duodenal varices verified by endoscopy** • **Hepatic encephalopathy, Grade ≥2** • **New onset ascites requiring treatment** • **Worsening of ascites (requiring increase in drug therapy or requirement of surgical procedure such as paracentesis or shunt placement)** • **Refractory ascites -unresponsive to medications, and patient is not a candidate for TIPS or shunt and requires large volume paracentesis** • **Hyponatremia (Na ≤125 mEq/L) secondary to ascites** • **Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis-by cell count/chemistry)** • **Hepatorenal syndrome Type 1 and Type 2 and Acute Kidney Injury (AKI)** • **Liver failure defined as worsening of liver synthetic function that is persistently worse relative to baseline and/or progressive over time:** – **Hepato-pulmonary syndrome** – **Porto-pulmonary syndrome** – **Liver Transplant** – **Increase in MELD scores by 3 points relative to baseline, persistent over time and unrelated to vitamin K deficiency related increase in INR**	

		– **Any liver related event that requires hospitalization and treatment**	
Section 13.1.4.1, Reporting of Adverse Events	Insertion	**In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any patient.**	Enhanced communication of the Investigator and Medical Monitor in the event of signs or symptoms of hepatic decompensation.
Section 13.1.8, Follow-Up of Adverse Events and Serious Adverse Events	AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. ~~If resolved, a resolution date for the AE should be documented on the eCRF.~~ The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator. All patients showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.	AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. The Investigator must ensure that follow up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator. **Drug-Induced Liver Injury or Disease Progression** All patients showing possible drug-induced liver injury **or disease progression** should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease. **Cholecystitis or Pancreatitis** **Patients should be instructed to contact the investigational site if they experience any of the following signs and symptoms: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, or weakness. Patients should also be counseled to seek immediate medical assistance if they experience persistent severe abdominal pain.** **In the event that cholecystitis and/or pancreatitis is suspected, Investigators should promptly bring patients into the clinic to undergo a complete**	Increased monitoring per standard of care if a patient is diagnosed or develops symptoms consistent with pancreatitis.

		evaluation, including a physical examination, and laboratory assessments [ie, amylase and lipase]). Investigators should refer to standard of care guidelines on suspected pancreatitis (Banks 2012, Greenburg 2015). Diagnosis of acute pancreatitis includes 2 of the following: **• Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)** **• Serum lipase activity (or amylase) at least 3 times greater than the upper limit of normal** **• Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging** **To ensure appropriate vigilance, amylase and lipase levels should be monitored monthly for 3 months after onset of symptoms, irrespective of whether a diagnosis of cholecystitis and or pancreatitis is confirmed. The Investigator should contact the Medical Monitor upon awareness of the above (ie, suspected or confirmed diagnosis).** Results should be recorded promptly in the eCRF.	
Section 13.1.9, Pregnancy and Follow-Up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must ~~interrupt~~ treatment with investigational product immediately (see Section 8.4.1.3) and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD. The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor. ~~The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The patient must have a negative pregnancy test before restarting investigational product. If a patient's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy confirmed by a serum β-hCG test before restarting investigational product.~~	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must **discontinue** treatment with investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.	Per new study-specific safety updates, pregnancy will require discontinuation and no option to restart.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 13.2.2., Medical and Surgical Procedures	New Section	**Medical and surgical procedures will be recorded at the visits indicated in Table 1.**	Section added for consistently with Schedule of Events.
Section 13.2.5, Electrocardiogram	Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time. ~~Full instructions will be provided for forwarding the ECGs for central reading.~~	Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time.	Correction.

<table>
<tr>
<td>Section 13.2.6, Laboratory Assessments</td>
<td>Table ~~9~~ List of Laboratory Analytes to be Tested
<table>
<tr><th>Laboratory Assessment</th><th>Analyte</th></tr>
<tr><td>Serum Chemistry</td><td>Albumin, blood urea nitrogen, creatinine~~, direct bilirubin, total bilirubin,~~ aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, TFT (TSH, free T3 and free T4)</td></tr>
<tr><td>Hematology</td><td>Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)</td></tr>
<tr><td>Coagulation</td><td>PT, PTT, INR</td></tr>
<tr><td>Urinalysis (dipstick)</td><td>pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, ~~albumin, creatine,~~ leucocytes, nitrates, albumin/~~creatine~~ ratio (if positive~~), pregnancy~~</td></tr>
<tr><td>~~Markers of Inflammation~~</td><td>~~IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30~~</td></tr>
<tr><td>Noninvasive measurements of liver fibrosis~~, liver stiffness and cirrhosis~~</td><td>ELF (HA, P3NP, and TIMP-1)
~~TE~~</td></tr>
<tr><td>PK assessments</td><td>OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)</td></tr>
</table>
</td>
<td>Table 11 List of Laboratory Analytes to be Tested
<table>
<tr><th>Laboratory Assessment</th><th>Analyte</th></tr>
<tr><td>Serum Chemistry</td><td>Albumin, blood urea nitrogen, creatinine, direct bilirubin, total bilirubin, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, total bilirubin, free fatty acids, TFT (TSH, free T3 and free T4)</td></tr>
<tr><td>Hematology</td><td>Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)</td></tr>
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<tr><td>Urinalysis (dipstick)</td><td>pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, leucocytes, nitrates; albumin, creatinine, albumin/creatinine ratio (if positive); β-hCG</td></tr>
<tr><td>Markers of Cholecystitis and Pancreatitis</td><td>Amylase and lipase</td></tr>
</table>
</td>
<td>Markers of inflammation samples were removed to simplify the study design.
Amylase and lipase added per FDA request.
Total OCA calculation update is a correction.</td>
</tr>
</table>

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
	<table><tr><td>PD markers</td><td>C4, FGF-19 and plasma bile acids</td></tr></table> … INR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, ~~Na,~~ and INR values, with modification by United Network for Organ Sharing. ~~Total OCA will be calculated based on OCA, tauro-OCA, glyco OCA, and metabolite OCA glucuronide concentrations.~~ Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.	<table><tr><td>Noninvasive measurements of liver fibrosis</td><td>ELF (HA, P3NP, and TIMP-1)</td></tr><tr><td>PK assessments</td><td>OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)</td></tr><tr><td>PD markers</td><td>C4, FGF-19 and plasma bile acids</td></tr></table> … NR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, and INR values, with modification by United Network for Organ Sharing. **Total OCA will be calculated based on the sum of OCA, glyco-OCA, and tauro-OCA concentrations**. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.	
Section 14.1.1, Child-Pugh Score	Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory. ~~Investigators will be responsible for determining the appropriate dosing regimen based on the CP score (and). Any change in CP Score will necessitate re evaluation of the dosing regimen.~~	Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory.	Per new dosing guidelines, CP score will not determine dosing regimen.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 14.1.2, Model of End Stage Liver Disease Score	An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival ~~and is calculated according to the following formula~~ (Kamath 2007): ~~MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43~~ ~~MELD score will be calculated and reported in whole numbers according to the frequency listed in Table 1.~~	An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival (Kamath 2007). **MELD score will be calculated and reported for visits where these parameters are measured (see Table 1).**	Text clarified since calculation is not performed by the site.
Section 14.2.1, Markers of Inflammation, Apoptosis and Necrosis	~~Markers of Inflammation, Apoptosis and Necrosis~~ ~~Blood samples for analytes including IL-6, hs-CRP, IgA, IgG, IgM, TNF-α, cytokeratin-18 neoepitope M30.~~ ~~Assessments will be performed according to the schedules presented in .~~	Deletion	Markers of inflammation were removed to simplify the study design.
Section 15.3, Pharmacokinetic Analyses	PK analysis will based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.	PK analysis will **be** based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics. **Full details regarding the planned analyses, methods, and outputs for the study will be detailed in the SAP.**	Clarification.
Section 15.4, Safety Analyses	Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. ~~CP scores will be summarized by treatment group at Baseline and at each post-Baseline visit.~~ No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.	Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.	Correction.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 15.4.1, Adverse Events	Insertion	**Adverse events of special interest as defined in Section 13.1.1.4 will be summarized for each treatment group.**	Per FDA request.
Section 15.4.2, Clinical Laboratory Evaluations	Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment. In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation. ~~Vital Signs and Weight~~ ~~The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.~~ ~~Electrocardiograms~~ ~~Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.~~	Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment. In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.	Correction. Moved to separate section since not laboratory evaluations.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 15.4.3, Additional Safety Analysis	New Section	**<u>Vital Signs and Weight</u>** **The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.** **<u>Electrocardiograms</u>** **Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.**	Separate section created per above deletion.
Section 15.5, Efficacy Analyses	Risk Scores: Changes from baseline in the MELD score and in CP score will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.	Risk Scores: Changes from baseline in the MELD score and in CP score**, C4, FGF-19 and plasma bile acids** will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.	Clarification.
Section 15.6, Additional Efficacy Analyses	Analyses of changes in liver stiffness and ELF~~, cytokeratin~~ and TIMP-1~~, and markers of inflammation~~ will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin. …	Analyses of changes in liver stiffness **(TE)** and **liver fibrosis (**ELF **[HA, P3NP,** and TIMP-1**])** will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin. … **Full details regarding additional efficacy analyses will be detailed in the SAP.**	Clarification

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 21, List of references	Insertion	**Banks O, Bollen T, Dervenis C, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62:102-111.** **…** **Greenburg J., Hsu J., Bawazeer M., et al. Clinical Practice Guideline: Management of acute pancreatitis. Can J Surg. 2016; 59 (2):128-140.** **…** **Kumar A, Saraswat VA. Hepatitis E and Acute-on-Chronic Liver Failure. Journal of clinical and experimental hepatology. 2013 Sep;3(3):225-30.** **…** **Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014 Aug;60(2):715-35.**	New references added per added cited content.

Clinical Study Protocol 747-401

OBETICHOLIC ACID (OCA)

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

Version 4: 15 Feb 2019

EudraCT Number: 2017-001762-13

Sponsor

Intercept Pharmaceuticals, Inc.
4760 Eastgate Mall
San Diego, CA 92121
USA

TEL: +1 858 652 6800

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD PhD

02/15/19

Date

Sr Vice President, Clinical Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-401. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected patients according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-401 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human patients in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

Medical Monitor

Primary Contact:	PPD Senior Medical Director, Clinical Division Syneos Health PPD PPD
Secondary Contact:	PPD DO, MSPH Senior Medical Director Intercept Pharmaceuticals, Inc. (Intercept) PPD
24-Hour Telephone:	PPD
SAE Fax:	PPD
SAE Email:	PPD

2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; (6-ECDCA)

Title of Study:

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

Investigators and/or Study Center(s):

The study is planned to have approximately 50 investigational sites, globally.

Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.	**Phase of Development:** Phase 4: US, Canada, and the EU Phase 3b: All other regions

Objectives:

Primary Objective:

- To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

Secondary Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - The model of end stage liver disease (MELD) score and its components
  - Child-Pugh (CP) score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

Additional Objectives:

- To evaluate the effect of OCA treatment compared to placebo on:
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD parameters and safety and tolerability assessments
- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ])

- To assess clinical events consistent with end-stage liver disease
  - Death (all-cause)
  - Liver transplant
  - MELD score ≥15 (for patients with MELD ≤12 at baseline)
  - 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
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

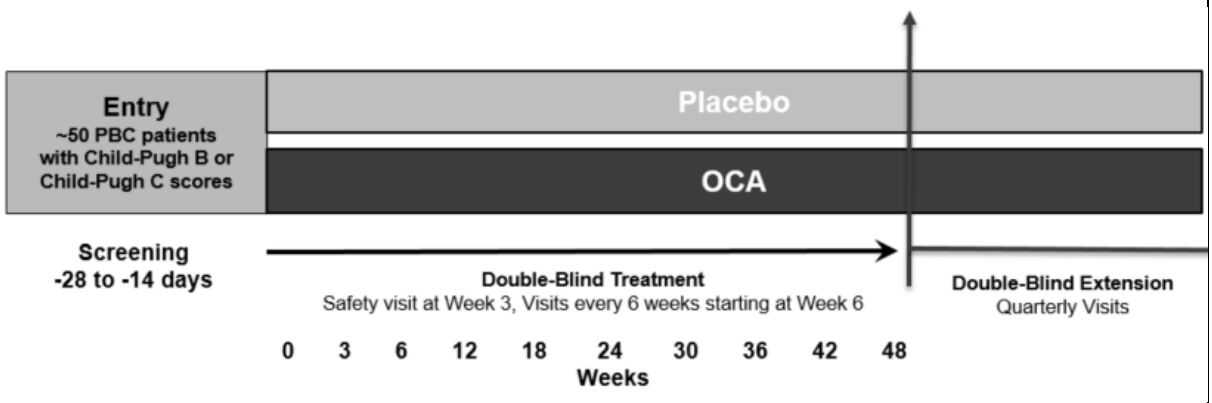
Methodology: This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with primary biliary cholangitis (PBC) and moderate to severe hepatic impairment defined as Child-Pugh B (CP-B) (moderate) and Child-Pugh C (CP-C) (severe) including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to one of two treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. Titration may be considered as early as the Week 12 Visit. Fasting PK assessments will be performed in all patients participating in the study on Day 1, Week 6, and Week 36. Serial PK sampling (which also includes a fasted PK assessment) will be performed at Week 12, 18, 24, 30, and 48.

Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

Study Design Diagram



OCA = obeticholic acid, PBC = primary biliary cholangitis

Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.

Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

Dosing Regimen:

All patients will initiate investigational product once weekly with 5 mg OCA or matching placebo. Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.

Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

Planned OCA or Matching Placebo Dosing Regimen

	Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)	
	Treatment Group	
	OCA	Placebo
Starting Dose (Day 1)	5 mg once weekly	matching placebo once weekly
Titration 1[a]	5 mg twice weekly[b]	matching placebo twice weekly[b]
Titration 2[a]	10 mg twice weekly[b]	matching placebo twice weekly[b]

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Number of Patients (planned): Approximately 50 patients will be enrolled in this study.

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines, defined as having ≥2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
    - Liver biopsy consistent with PBC (collected at any time prior to Screening)
2. Evidence of cirrhosis including at least one of the following:
    - Biopsy results consistent with PBC Stage 4
    - Liver stiffness as assessed by TE Value ≥16.9kPa
    - Clinical evidence in the absence of acute liver failure consistent with cirrhosis including: gastroesophageal varices, ascites, radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
    - Combined low platelet count (<140 000/mm^3) with
        - persistent decrease in serum albumin, or
        - elevation in prothrombin time/INR (not due to antithrombotic agent use), or
        - elevated bilirubin (2× ULN)
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening:
    - Moderate: CP-B (Scores 7 to 9) or
    - Severe: CP-C (Scores 10 to12)
4. MELD score of 6 to 24 at Screening
5. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate or unresponsive to UDCA (no UDCA for ≥3 months)

Key Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. Current hepatic encephalopathy (as defined by a West Haven score of ≥2)
5. History or presence of other concomitant liver diseases including:
    - Hepatitis C virus infection and RNA positive
    - Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the Medical Monitor
    - Primary sclerosing cholangitis
    - Alcoholic liver disease
    - Definite autoimmune liver disease or overlap hepatitis
    - Gilbert's Syndrome

6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function prior to randomization

Investigational Product, Dosage and Mode of Administration:

OCA 5 mg or OCA 10 mg tablets, oral administration

Placebo tablets, matched in size and appearance to OCA tablets, oral administration

Duration of Treatment:

Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

Criteria for Evaluation:

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus, and fatigue
Secondary Objectives	**Assessments**
Changes in risk scores	Changes in MELD and in CP scores and components of the CP score and MELD score
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma bile acids
Additional Objectives	**Assessments**
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	TE and ELF (HA, P3NP, and TIMP-1)
PK/PD relationship	PK parameters compared to PD parameters and safety and tolerability assessments (above)
Patient-reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
Clinical events	Death (all-cause and liver-related), liver transplant, MELD score ≥15 (for patients with MELD ≤12 at baseline), hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and HCC.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; INR = international normalized ratio; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PBC = Primary Biliary Cholangitis; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TE = Transient Elastography; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; VAS = visual analog scale

Statistical Methods:

Analysis Populations:

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK Population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

Pharmacokinetic Analyses:

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, metabolite OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.

Safety Analyses:

Safety analyses will be conducted using the Safety population. Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group. The incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs) will be tabulated by system organ class and preferred term for each treatment group, and similarly by severity and relationship to treatment. Laboratory parameters, physical examinations including vital signs, and electrocardiograms will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.

Efficacy Analyses:

This study does not plan to conduct a formal hypothesis testing for any efficacy endpoint.

The endpoints of efficacy assessments are change in total and direct bilirubin, INR, creatinine, albumin, platelets, ALP, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline values as covariates. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Additional Efficacy Analyses

Analyses of changes in liver stiffness (TE) and liver fibrosis (ELF [HA, P3NP, and TIMP-1]) will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.

The following endpoints consistent with end-stage liver disease will be captured in the study:

- Time to death (all cause)
- Time to liver-related death
- Time to liver transplant
- MELD score ≥15 (for patients with MELD ≤12 at baseline)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Time to variceal bleed

- Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)
- Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)

- Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

The incidence and time to first occurrence of any of the above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of HCC will be summarized by treatment group using the same methods as defined above.

Sample Size Justification:

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. A total of 30 patients is adequate with 10 patients on placebo to be included as a comparator and 20 patients on OCA. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Placebo and OCA.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
6-ECDCA	6α-ethyl chenodeoxycholic acid (also known as INT-747)
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
BP	blood pressure
C4	7α-hydroxy-4-cholesten-3-one
CAC	Cardiovascular Adjudication Committee
CI	confidence interval
CLDQ	Chronic Liver Disease Questionnaire
CRA	Clinical Research Associate
CP	Child-Pugh
eCRF	electronic case report form
DDI	drug-drug interaction
DMC	Data Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation or Specialist Term	Explanation
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid
HCC	hepatocellular carcinoma
HCP	health care professional
HDL	high-density lipoprotein
IB	Investigational Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
ITT	intent-to-treat
IWRS	interactive web response system
KM	Kaplan-Meier
LDL	low-density lipoprotein
LTSE	long-term safety extension
LS	least squares
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model of end stage liver disease
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SD	standard deviation
SEM	standard error of the mean
SI	standard international system of units
SOC	system organ class

Abbreviation or Specialist Term	Explanation
StdErr	standard error
SUSAR	suspected unexpected serious adverse reaction
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
the Sponsor	Intercept Pharmaceuticals, Inc.
TIPS	transjugular intrahepatic portosystemic shunt
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
US	United States (of America)
VAS	visual analogue scale
VLDL	very low-density lipoprotein

5. INTRODUCTION

5.1. Overview of Disease State and OCA

Primary biliary cholangitis (PBC, also known as primary biliary cirrhosis [Beuers 2015a, Beuers 2015b, Beuers 2015c]) is a serious, life-threatening, cholestatic liver disease of unknown etiology that, without treatment, frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and necessitates liver transplantation or results in death. PBC is a rare disease with reported prevalence in the US of 40.2/100 000 (Kim 2000). PBC disproportionately affects women approximately 10:1 and is typically diagnosed in patients between 40 to 70 years of age.

Historically, the only approved drug therapy for PBC has been the bile acid, ursodeoxycholic acid (UDCA), a physiological constituent of human bile (Lindor 2009). While UDCA therapy had a marked effect on the treatment of PBC, up to 50% of patients showed a suboptimal response or no response to UDCA. Such patients were at significantly increased risk of a poor clinical outcome due to PBC disease progression.

Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist and modified bile acid derived from the primary human bile acid chenodeoxycholic acid (CDCA) (Pellicciari 2002), was developed for the treatment of PBC and to provide patients who have an inadequate response to or poor tolerance of UDCA a novel treatment option that was safe and effective.

In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication, and in May 2017 Ocaliva received approval from Health Canada. Since then, other countries have received approval (eg, Australia and Switzerland). Study 747-401 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC; in all other regions, this study is considered Phase 3b.

5.2. Nonclinical Experience with Obeticholic Acid

Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.

5.3. Clinical Development of Obeticholic Acid

As of 28 October 2018, approximately 3470 subjects have received ≥ 1 dose of OCA. This estimation includes subjects from blinded ongoing studies. Of these 3470 subjects, 888 were healthy volunteers, 580 subjects had PBC, 72 subjects had PSC, 6 subjects had biliary atresia, 41 subjects had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 1914 subjects had NASH, and 33 subjects had portal hypertension due to alcoholic cirrhosis.

Overall, the pharmacokinetic (PK) profile of OCA is consistent with that expected of a bile acid. Phase 1 studies demonstrated that OCA is rapidly absorbed and extensively conjugated with

glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates are primarily eliminated via biliary excretion, and plasma concentration time profiles demonstrated multiple peaking with prolonged exposure, indicative of enterohepatic circulation. Plasma concentrations of OCA and its conjugates spike shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.

The OCA clinical development PBC program was based on a wide range of studies in PBC patients and healthy volunteers. The clinical pharmacology studies supported the proposed dosing regimen: 10 mg fixed dose and a titration regimen starting at OCA 5 mg with titration to 10 mg based on clinical and biochemical response. The clinical program included a pivotal Phase 3 clinical study (747-301) and two Phase 2 clinical studies (747-201 and 747-202), which formed the primary basis of approval of OCA.

Study 747-201 (59 patients) evaluated 2 doses of OCA (10 mg and 50 mg) given as monotherapy versus placebo. Statistically significant and clinically relevant relative and absolute reductions from Baseline in alkaline phosphatase (ALP) were achieved with both doses of OCA versus placebo ($p < 0.0001$). Mean relative ALP reductions were 45% (OCA 10 mg) and 38% (OCA 50 mg) compared to an increase of 0.4% with placebo. Further, significant improvements in gamma-glutamyl transferase (GGT) and in conjugated bilirubin were observed with both doses compared with placebo ($p < 0.05$). OCA also resulted in decreased circulating alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

Study 747-202 (165 patients) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in patients on a stable therapeutic dose of UDCA. Overall, the data from 747-202 were consistent with Study 747-201. Statistically significant and clinically meaningful relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p < 0.0001$). Mean ALP reductions from baseline ranged from 21% to 25% compared to 3% with placebo. Improvements were also seen in GGT and ALT levels and in conjugated bilirubin levels.

Study 747-301 (216 patients) was a Phase 3, double-blind, placebo-controlled, parallel-group study followed by a long-term safety extension (LTSE) using OCA in patients with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of patients reaching specific criteria for ALP and bilirubin (ALP <1.67x upper limit of normal [ULN] with a ≥15% reduction and bilirubin ≤ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to <1.67x ULN with a ≥15% reduction from baseline and a normal bilirubin level after 12 months of therapy. The placebo group experienced a least squares (LS) mean decrease in ALP from baseline of 5%, compared to a significant LS mean decrease of 39% in the OCA 10 mg dose group and 33% in the OCA titration group (both OCA dose groups $p < 0.0001$ versus placebo).

The LTSE phases of both Phase 2 studies and the pivotal Phase 3 study support the long-term safety of OCA and demonstrate a durable therapeutic response.

Study 747-302 is an ongoing randomized, double-blind, placebo-controlled clinical outcomes study, designed to confirm the clinical benefit of OCA treatment in patients with PBC. This study is inclusive of patients with early to advanced stage PBC.

5.4. Rationale for Study Design and Dose for Investigational Product

5.4.1. Rationale for Study Design

There are limited clinical data available to support the use of OCA in patients with PBC with moderate to severe hepatic impairment. The current recommended dosing of such patients is based on modeled systemic and hepatic concentrations. Therefore, Study 747-401 is specifically designed to characterize the PK, safety, and efficacy of OCA in this patient population.

PK and safety parameters will be evaluated as the primary objectives and efficacy parameters will be evaluated as secondary and additional objectives. While the prognostic utility of ALP has been established by the Global PBC study group, increasing levels of bilirubin are more relevant to understanding the progression of end stage liver disease. Consistently, bilirubin is a key marker of advancing disease as characterized by the Global PBC study group as well as its incorporation into model of end stage liver disease (MELD), Child-Pugh (CP), and Mayo risk scores. As such, the potential of OCA to stabilize bilirubin levels will be evaluated.

In order to generate data for the patient population in a timely fashion, Study 747-401 is designed with a relatively short-term, 1-year double-blind treatment period to gather primarily PK and safety data. Therefore, the study will not formally test the long-term efficacy of OCA on clinical outcomes.

Although Study 747-401 is not designed to formally evaluate clinical outcomes, these data will be collected and assessed as an additional objective. Given the importance of evaluating clinical outcomes in patients with the most advanced form of the disease, these events will be prospectively adjudicated consistent with the procedures implemented in ongoing PBC studies. This will allow for a more robust meta-evaluation of clinical outcomes in patients with moderate to severe hepatic impairment following the completion of both studies.

Study 747-302 is specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment. Data collected from Study 747-401 will serve as a bridge to the 747-302 study.

Taken together, data from this study will complement the data from Study 747-302 and offer the opportunity to better inform the benefit risk profile and appropriate treatment of hepatically-impaired patients.

5.4.2. Rationale for Obeticholic Acid Dose and Duration

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (CP Score). Model simulations predicted that for mild (Child-Pugh A [CP-A]), moderate (Child-Pugh B [CP-B]), and severe (Child-Pugh C [CP-C]) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to patients with normal hepatic function, whereas total OCA liver concentrations increase 1.1-, 1.5-, and 1.7-fold, respectively. Because the liver is the primary site of action for the safety and efficacy of OCA, it is important to account for the differences in systemic and liver exposure when assessing effective doses. It is also important to note that while hepatically impaired (CP-B and C) patients treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy patients, no apparent impact on the overall safety profile was observed, consistent with only a modest

increase in liver exposure of OCA associated with hepatic impairment. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).

5.4.3. Rationale for Population Chosen

Patients with PBC and moderate or severe hepatic impairment, based on CP score and varying levels of MELD, are the targeted population for this study as OCA has been studied primarily in early to moderate stages of liver impairment in patients with PBC. There is a great need to extend therapies to PBC patients with more advanced liver impairment. Given the unmet medical need and observed efficacy, safety and tolerability profile of OCA in early and moderate PBC, evaluating the effects of OCA in a late stage population is warranted.

5.4.4. Rationale for Control Group

The use of a randomized placebo control group added to established standard of care provides the best scientific evidence of efficacy and safety. The use of a placebo control provides a concurrent comparator group, accounting for not only a placebo effect but continued standard of care. The use of a placebo control is critical to assess the safety and tolerability of OCA but also as a comparator for the high rate of clinical events which are expected in this advanced population.

5.5. Importance of Monitoring of Disease Progression

Given PBC is a chronic, progressive liver disease, it is important that patients with PBC are closely monitored to ensure early identification of decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve patient oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual patients to determine on an ongoing basis the totality of a patient's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring.

Patients will be monitored for potential hepatic injury and/or decompensation. Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 8.4 and Section 7.6. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.

5.6. Summary of Known Potential Risks with Investigational Product

The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk.

Clinical Data

In two Phase 2 studies and a Phase 3 study evaluating OCA in the treatment of subjects with PBC, hepatic adverse events were observed in subjects receiving doses of OCA ranging from the maximum approved dose of 10 mg once daily to 50 mg (5 times the highest recommended dose).

Ongoing NASH clinical trials include reports of hepatic decompensation assessed as suspected unexpected serious adverse reactions (SUSARs). Data remain blinded. Additional details of these SUSARs are provided in the IB Version Number: 18 (31 January 2019).

The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease.

Changes in lipid profiles have also been observed with OCA dosing, including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further.

An independent data monitoring committee (DMC) has performed detailed reviews of ongoing studies of obeticholic acid, including the Phase 3/4, clinical outcomes study in PBC (747-302), this Phase 4 PK and safety study in patients with PBC (747-401), the Phase 3, pivotal study in NASH with fibrosis (747-303), and the Phase 3 study in NASH with cirrhosis (747-304). The DMC will continue to review data quarterly and will provide oversight of the above-mentioned studies throughout the course of the development program. Additional details are provided in IB Version Number: 18 (31 January 2019).

Post-Marketing Cases in PBC

As of October 2018, greater than 4200 patients have received Ocaliva® in the post-marketing setting. In patients with moderate to severe hepatic impairment (Child-Pugh B and C), liver decompensation, liver failure, and death have been reported when Ocaliva was dosed up to 7 times the recommended once weekly starting dose for such patients. Based on the initial medical assessment of these cases, which included patients having undergone liver transplant, there was insufficient evidence suggesting a causal relationship between higher than recommended dosing and the reported adverse events. However, Intercept Pharmaceuticals, Inc. (the Sponsor) continues to assess the potential association between adverse events, including deaths, and the higher than recommended dosing of Ocaliva observed in PBC patients with moderate to severe hepatic impairment (Child-Pugh B and C) through ongoing post-marketing pharmacovigilance activities.

Signs and symptoms reported in patients experiencing liver-related adverse events who received Ocaliva include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new

or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice, and liver decompensation.

Refer to the IB for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

The study will be conducted in patients with PBC and moderate to severe hepatic impairment defined as CP-B and CP-C with MELD scores ranging from 6 to 24.

6.1. Primary Objectives

- To evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and OCA metabolite glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

6.2. Secondary Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - The MELD score and its components
  - CP score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

6.3. Additional Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD parameters and safety and tolerability assessments
- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ]

- To assess clinical events consistent with end-stage liver disease
  - Death (all cause)
  - Liver transplant
  - MELD score ≥15 (for patients with MELD ≤12 at baseline)
  - 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
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 4, randomized, double-blind, placebo-controlled study will evaluate the PK and safety of OCA treatment in patients with PBC and moderate to severe hepatic impairment defined as CP-B and CP-C including a broad distribution of MELD scores (ranging from 6 to 24). Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to 1 of 2 treatment groups: Placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

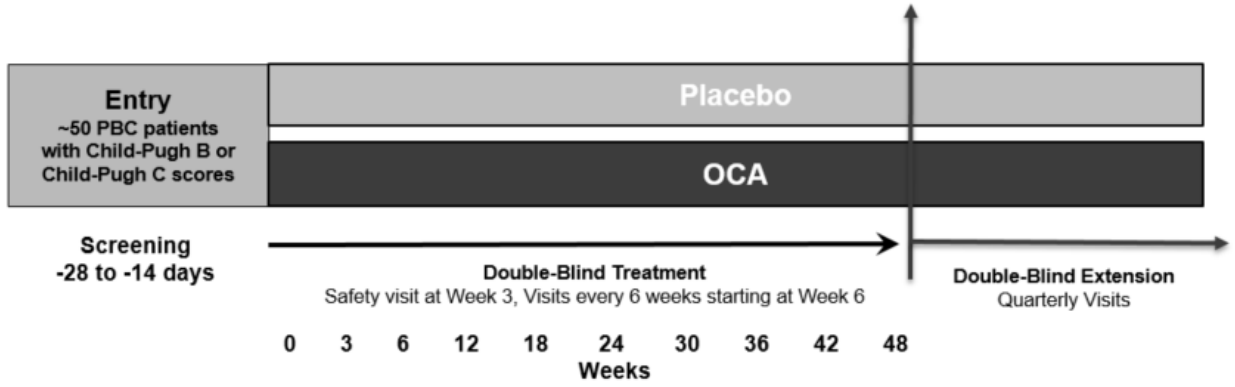
Following completion of safety assessments and laboratory specimen collection, blinded investigational product will be dispensed with instruction to begin dosing the same day (Day 1) at OCA 5 mg or placebo once weekly.

Double-Blind Treatment Period: During the 48-week treatment period, an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. Titration may be considered as early as the Week 12 Visit (see Section 7.3). Fasting PK assessments will be performed in all patients participating in the study on Day 1, Week 6, and Week 36. Serial PK sampling (which also includes a fasted PK assessment) will be performed at Week 12, 18, 24, 30, and 48.

Patients who have completed their 48-week, double-blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

7.1.1. Study Design Diagram

Figure 1: Study Design



OCA = obeticholic acid, PBC = primary biliary cholangitis

Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.

Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

			Double-Blind Treatment Period (Weeks)[b]									Double-Blind Extension
	Screening	**Day 1[a]**	**3[c]**	**6[d]**	**12**	**18**	**24**	**30**	**36**	**42[c]**	**48/ ET/ EOS/EOT**	**Every 3 months**
Visit Window (+/-)	**-28 to -14 days**		**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±2 wks**
Fast ≥8 h Prior to Visit[e]	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent	X											
Medical/PBC History	X											
Inclusion/Exclusion Criteria	X	X										
Physical Exam[f]	X	X		X	X	X	X	X	X		X	X
Vital Signs and Weight	X	X		X	X	X	X	X	X		X	X
Medical and Surgical Procedures		X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Assessments for Child-Pugh Score[g]	X	X		X	X	X	X	X	X		X	X
Patient Questionnaires (Pruritus VAS, PBC-40, EQ- 5D-5L, and CLDQ)[h]		X		X	X	X	X	X	X		X	X
Randomization/Treatment Assigned		X										
Dispense IP[i]		X			X	X	X	X	X	X	X	X
Dose Titration Assessment[j]					X	X	X	X	X	X	X	X
IP Accountability/ Compliance			X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Study Procedures (Continued)

			Double-Blind Treatment Period (Weeks)[b]									Double-Blind Extension
	Screening	**Day 1[a]**	**3[c]**	**6[d]**	**12**	**18**	**24**	**30**	**36**	**42[c]**	**48/ ET/ EOS/EOT**	**Every 3 months**
Visit Window (+/-)	**-28 to -14 days**		**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±2 wks**
Urinalysis	X	X									X	X[p]
Urine-based β-hCG Pregnancy Test[k]	X	X		X	X	X	X	X	X		X	X
Virology (HCV/HBsAg)	X											
Serum Chemistry/Hematology/ Coagulation[l]	X	X	X	X	X	X	X	X	X	X	X	X
Amylase and Lipase	Sample to be collected if the patient experiences acute pancreatitis or cholecystitis.											
PK Fasting Collection		X		X					X			
PK Serial Collection[m]					X	X	X	X			X	
PD Markers: Bile Acid/C4/FGF-19		X		X	X	X	X	X	X		X	
TE/ELF (HA, P3NP, and TIMP-1)[n]		X			X		X		X		X	X[o]
12-Lead Electrocardiogram	X										X	X[p]
Hepatic Ultrasound[q]	X[r]	X[s]					X				X	X[o]
Gallbladder assessment (ultrasound)	X[r]	X[s]										

AE = adverse event; eCRF = electronic case report form; C4 = 7α hydroxy-4-cholesten-3-one; CLDQ = Chronic Liver Disease Questionnaire; ELF = enhanced liver fibrosis; ET = Early Termination; EOS = End of study; EOT = End of Treatment; ; FGF-19 = fibroblast growth factor-19; HA = hyaluronic acid; HCV = Hepatitis C virus; IP = Investigational Product; P3NP = procollagen 3 N-terminal peptide; PBC = primary biliary cirrhosis; PK = pharmacokinetics; TE = transient elastography; wk(s) = week(s), TIMP-1 = tissue inhibitor of metalloproteinase ; VAS = Visual Analogue Scale.

[a] Visit schedule should be based on Day 1. Day 1 visit must occur at least 2 weeks after screening visit.

[b] Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 9 and continuing to Week 48 to assess for AEs, concomitant medications, medical/surgical procedures, and verify that s/he is dosing as directed. (see Section 9.7.8).

[c] Preferably, the patient comes in to the clinic for this visit. Alternatively, site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.

[d] Visit should occur 3, 4, or 5 days after taking the Week 6 dose.

[e] The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, including screening, but water is permitted.
[f] Height and assessment of smoking and alcohol consumption history and current habits will be assessed at Screening and Week 48. Assessment of smoking and alcohol consumption history and current habits will be assessed quarterly after Week 48.
[g] Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF.
[h] The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease.
[i] New investigational product bottles will be dispensed if the patient is up-titrated. Unless up-titrated, patients are expected to use up each investigational product bottle before a new bottle will be dispensed. No new bottles will be dispensed if dose frequency is changed. Patients will be instructed to begin dosing on Day 1, after completing all study assessments. Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.
[j] Dose titration of investigational product may occur starting after the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.
[k] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit (except Week 3). If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally).
[l] MELD values will be calculated based on serum chemistry and coagulation values at each visit.
[m] The patient will be given the option to return to the clinic the following morning for the 24-hour postdose PK sample or samples can be obtained by a home health care designee. Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling.
[n] The noninvasive radiological liver fibrosis measurement devices (such as, FibroScan® device [Echosens; Paris, France]) will be used at all study sites to collect hepatic stiffness measurements.
[o] Patients will complete a TE/ELF and ultrasound assessment, every 6 months (±2 weeks) after Week 48.
[p] ECG and urinalysis will be done yearly (±2 weeks) after Week 48 Visit.
[q] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 1) ultrasounds: Unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm suspected HCC.
[r] If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required.
[s] If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.

7.1.3. Study Duration

Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week, double-blind treatment period will continue double-blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.

7.2. Number of Patients

Approximately 50 patients will be enrolled in this study.

7.3. Planned Dosing Regimen

All patients will initiate investigational product once weekly with OCA 5 mg or matching placebo (Table 2). Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below (Table 2). At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.

Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

Table 2: Planned OCA or Matching Placebo Dosing Regimen

	Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)	
	Treatment Group	
	OCA	**Placebo**
Starting Dose (Day 1)	5 mg once weekly	matching placebo once weekly
Titration 1[a]	5 mg twice weekly[b]	matching placebo twice weekly[b]
Titration 2[a]	10 mg twice weekly[b]	matching placebo twice weekly[b]

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

7.4. Monitoring and Management of Potential Hepatic Injury and/or Disease Progression

Given the chronic nature of PBC, it is important to monitor for potential hepatic injury, disease progression and/or hepatic decompensation. Child-Pugh and MELD scores will be reviewed at each visit where labs are drawn (Table 1). In addition, adverse events, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.2. Based on biochemical and clinical assessments, the investigational product may be interrupted or discontinued per criteria discussed in

Section 7.4.2 and Section 7.4.3, and close monitoring procedures will be implemented (refer to Section 7.6).

7.4.1. Signs and Symptoms of Potential Hepatic Injury or Decompensation

Patients should be instructed to contact study personnel if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting

Signs and Symptoms of Hepatic Injury or Decompensation:

- Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark] (reflecting impaired bilirubin metabolism)
- More general signs and symptoms of ascites and encephalopathy: confusion, swelling of the legs or abdomen
- Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite
- Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea for more than 4 days) and should be an indication for prompt investigational product interruption and complete patient evaluation

Other Symptoms:

- Worsening of renal function or likely dehydration

Healthcare Provider (HCP) Interactions:

- Visits to primary HCP or referral to any specialist for any new symptoms (other than ongoing care for stable comorbidities)
- New medications or changes to current medications prescribed from HCP or any new over the counter medications or herbal supplements
- Laboratory procedures or assessments performed by an HCP

Signs and symptoms for potential hepatic injury or decompensation should be followed by (1) evaluation of liver biochemistry for suspected drug-induced liver injury (DILI) or potential hepatic decompensation (Section 7.4.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.4.3), (3) triggering of close monitoring or investigational product interruption/discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 13.1), and (5) contact with the Medical Monitor.

7.4.2. Liver Biochemistry Assessments for Potential Hepatic Injury or Hepatic Decompensation

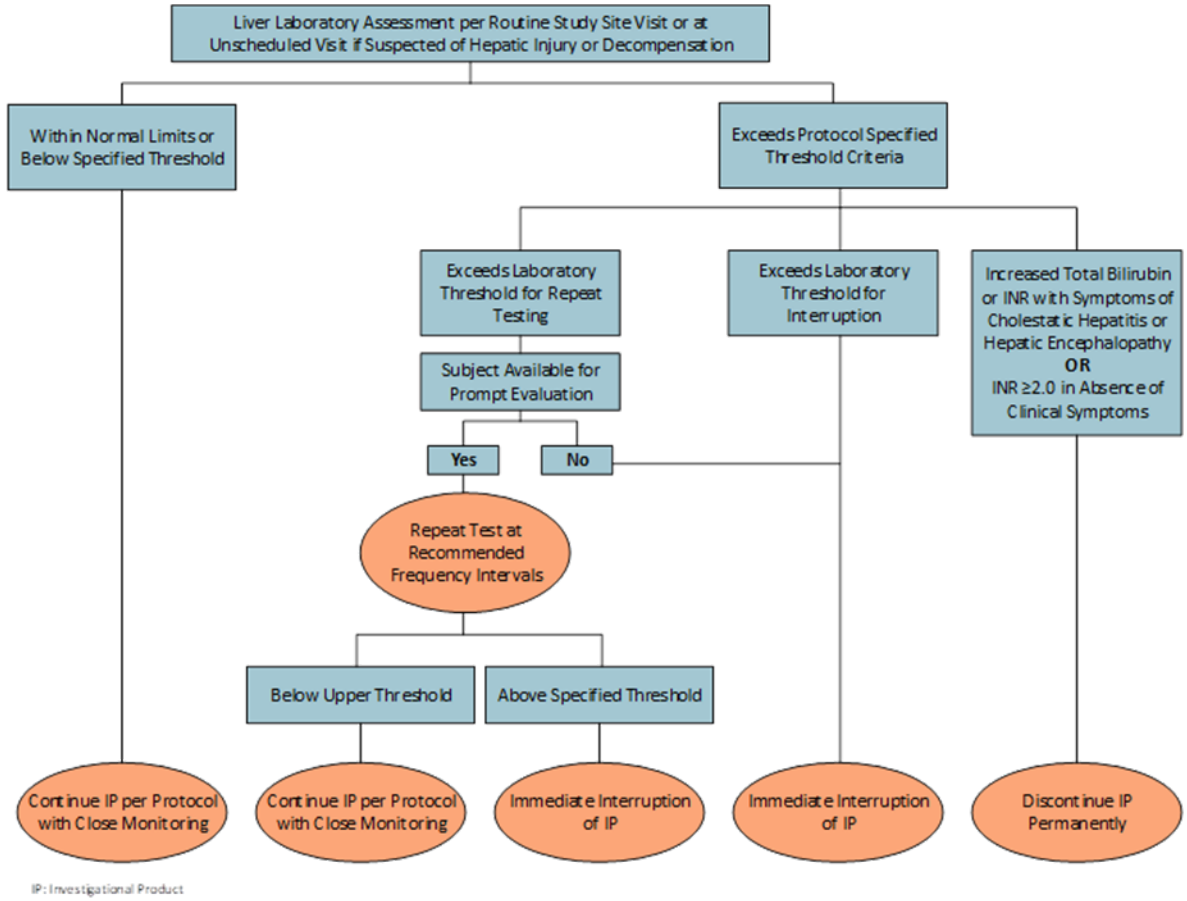
Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of patients for potential hepatic injury or hepatic decompensation. These assessments will be performed at:

- Each protocol-specified visit (Table 1)
- Unscheduled visits as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered

It is important that the laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. In the event that a patient cannot return to the clinic for a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local lab is permissible at the discretion of the Investigator. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges.

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and, potentially, a complete patient evaluation (depending on the repeat result) are summarized in Table 3.

Figure 2: DILI Management Algorithm



DILI = drug-induced liver injury; IP = Investigational Product

NOTE Other laboratory criteria include: ALT, AST, total bilirubin, INR, and electrolytes (sodium).

Table 3: Liver Laboratory Criteria for Monitoring of Suspected Hepatic Injury or Potential Hepatic Decompensation and Criteria for Interruption or Discontinuation of Investigational Product

Laboratory Criteria for Monitoring Suspected Hepatic Injury		
Laboratory Parameter	**Action Taken**	**Rechallenging Criteria**
Total Bilirubin		If a patient interrupts IP, they may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.
Baseline ≤ULN and ≥3x baseline	Interrupt IP	
Baseline >ULN and ≥2x Baseline	Interrupt IP	
ALT or AST		
>3x baseline (and >ULN)	Interrupt IP	
≥2x baseline	Repeat Test in 2 to 3 days, interrupt IP if still elevated	
Electrolytes[a]		
Sodium <130 mEq/L	Repeat Test in 2 to 3 days, interrupt IP if still below limit	
Laboratory Criteria for Monitoring Potential Hepatic Decompensation (Absence of Clinical Symptoms)		
Total Bilirubin Baseline ≤ULN and 1.5 mg/dL increase from baseline Baseline >ULN and 1.0 mg/dL increase from baseline	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt IP.	The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator. If laboratory values do not normalize, IP should not be restarted.
INR[b]		
>0.3 increase from baseline	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt IP.	The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator. If laboratory values do not normalize, IP should not be restarted.
≥2.0 unless due to vitamin K deficiency	Discontinue IP permanently	Continue to return for scheduled study visits for safety follow up. Monitor closely for clinical outcomes per protocol.
Laboratory Criteria for Monitoring Potential Hepatic Decompensation in the Presence of Clinical Symptoms		
Total bilirubin thresholds defined in Part B OR an INR increase from baseline of ≥1.5 are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy[c]	Discontinue IP permanently	Continue to return for scheduled study visits for safety follow up. Monitor closely for clinical outcomes per protocol.

IP = investigational product
[a] Sodium will be measured as an assessment of liver failure (hyponatremia).
[b] Does not apply in patients on anti-coagulants.
[c] Symptoms of cholestatic hepatitis includes dark urine and jaundice. Symptoms of hepatic encephalopathy may include lack of awareness, shortened attention span, lethargy, gross disorientation, or coma (unresponsive to verbal or noxious stimuli).

It should be noted that it is difficult to recognize every potential marker of hepatic or renal deterioration. There is no substitute for good medical judgment. Investigators will be reminded to be cautious and mindful in their evaluation of patients' symptoms, signs, and laboratory results. However, for example, a single abnormal laboratory analyte result may be artefactual; accordingly, Investigators will be allowed to implement an alternate follow-up procedure if considered appropriate based on their medical judgement, but only after documented agreement with the Sponsor's Medical Monitor.

7.4.3. Clinical Criteria for Monitoring for Potential Hepatic Decompensation

Patients will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 4.

Investigational product should be discontinued permanently if the patient received a liver transplant or experiences multi-organ failure as defined in Table 4, Part A. Patients should continue to return for scheduled study visits for safety follow-up.

Patients who experience other potential hepatic decompensation events defined in Table 4, Part B should be closely monitored until normalization or stabilization. Patients may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.

Table 4: Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Interruption / Discontinuation of Investigational Product

Hepatic Decompensation Events Requiring Mandatory Discontinuation of Investigational Product	
Decompensation Event	**Action Taken / Rechallenging Criteria**
Liver Transplant Multi-organ failure requiring hospitalization	Discontinue IP permanently and follow patients until normalization/stabilization. Continue to return for scheduled study visits for safety follow up.
Hepatic Decompensation Events Requiring Interruption of Investigational Product	
1. Liver failure defined as worsening synthetic function that is persistently worse relative to baseline and/or progressive over time (see Table 3, Part B)[a] 2. Variceal bleeding or recurrent variceal bleeding[b] documented by endoscopy or accompanied by anemia or melena with a hemoglobin drop of ≥2 g/dL 3. Ascites[c] including: 1. Worsening – requires increase in drug therapy or surgical intervention (paracentesis or shunt procedure) 2. Refractory ascites – unresponsive to medication; patient not candidate for transjugular intrahepatic portosystemic shunt (TIPS) or shunt; requires large volume paracentesis 3. Hyponatremia (≤125 mEq/L) secondary to ascites 1. Spontaneous Bacterial Peritonitis 2. Hepatic Encephalopathy, Grade ≥2 3. Any liver-related event requiring hospitalization and treatment (except multi-organ failure) 4. Hepatorenal syndrome Type 1 or Type 2 and acute kidney injury, hepatopulmonary syndrome, or portopulmonary syndrome	Closely monitor until normalization or stabilization. The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator IP should be re-initiated at a lower dose (or lower dose frequency) and titrated per Investigator discretion.

[a] Patients experiencing INR ≥2.0 unless due to vitamin K deficiency should be discontinued from IP permanently without rechallenge and should to return for scheduled study visits for safety follow up.
[b] Endoscopic confirmation of gastric or duodenal varices without evidence of bleeding should be closely monitored; investigational product may be interrupted at Investigator discretion
[c] New onset ascites requiring treatment should be closely monitored; investigational product may be interrupted at Investigator discretion

7.5. Dose Titration Criteria

Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns.

Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as assessed by a review of AEs and safety laboratory results). In general, down-titration may be done in response to tolerability concerns and can occur at any time.

Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated as defined in Section 7.3.

Scheduled Dose Titration - After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose for patients may occur no earlier than 6 weeks following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability).

7.5.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. To determine if a patient is eligible for a dose titration refer to Section 7.3.

7.6. Close Observation

If investigational product is interrupted or discontinued as described in Section 8.4, patients should be closely monitored (contacted by the site a minimum of every 2 weeks and scheduled visits every 6 weeks; if returning to the site for a scheduled visit is not feasible, use of a local lab may be permissible at the Investigator's discretion). At a minimum, the following assessments should be conducted at each study visit:

- Physical exam and thorough review of patient reported signs and symptoms,
- Liver biochemistry (including ALP, ALT, AST, GGT, total and conjugated bilirubin, creatinine, and albumin), prothrombin time (PT)/INR, serum electrolytes, and assessment of Child Pugh (only if the patient is at the study site) and MELD scores.

In addition, a trough pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any patient who develops an AE that is indicative of or consistent with hepatic injury or decompensation.

The following additional monitoring procedures should be performed for events of potential hepatic injury (per FDA Guidance for Industry on Drug Induced Liver Injury) or suspected hepatic decompensation based on criteria described in Section 7.4.1, Section 7.4.2, and Section 7.4.3. These cases need to be discussed with the Sponsor's Medical Monitor:

- Repeating liver biochemistry and function tests as described in Section 7.4.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic, as clinically indicated.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs potentially hepatotoxic, continued use of investigational

product should be discussed with the Sponsor's Medical Monitor. The patient may be discontinued from investigational product, if clinically appropriate.

- Obtaining a history of exposure to environmental chemical agents or herbal supplements which may be associated with liver toxicity.
- Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute HBV infection), and E; autoimmune or alcoholic hepatitis; Wilson's disease, hypoxic/ischemic hepatopathy; and biliary tract disease.
- Investigators should consider testing for Hepatitis E virus when assessing for hepatic decompensation as infection with Hepatitis E virus in patients with chronic liver diseases such as PBC may rapidly worsen with signs and symptoms similar to drug induce liver injury (Kumar 2013)
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Seeking hepatology consultation, if the Investigator is not a hepatologist

7.7. Criteria for Study Termination

The Sponsor (Intercept Pharmaceuticals, Inc.) reserves the right to terminate the study at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the Data Monitoring Committee (DMC), it may be necessary to stop the study before all patients have completed the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, Good Clinical Practice [GCP] noncompliance or poorly performing sites, as determined by the number of patients enrolled or the quality of the study data).

The Investigator and/or Sponsor (or designee) must notify the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of discontinuation of a site or the study and the reason for doing so.

Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all patients for the end of study (EOS) or end of treatment (EOT) Visit.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Patient Population

This study will be conducted at approximately 50 international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B and CP-C. Prospective patients will be identified primarily from the hospital and/or physician's database of patients with PBC, or may be referred from other physicians. Patients may self-refer to an Investigator if they become aware of the study through local, national, or international PBC patient societies, forums, or networks.

8.2. Patient Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines [Lindor 2009, EASL 2009]), defined as having ≥2 of the following 3 diagnostic factors:
   - History of elevated ALP levels for at least 6 months
   - Positive antimitochondrial antibody (AMA) titer or if AMA negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
   - Liver biopsy consistent with PBC (collected at any time prior to Screening)
2. Evidence of cirrhosis including at least one of the following:
   - Biopsy results consistent with PBC Stage 4
   - Liver stiffness as assessed by TE Value ≥16.9 kPa
   - Clinical evidence in the absence of acute liver failure consistent with cirrhosis including: gastroesophageal varices, ascites, radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
   - Combined low platelet count (<140 000/mm^3) with:
     - persistent decrease in serum albumin, or
     - elevation in prothrombin time /INR (not due to antithrombotic agent use), or
     - elevated bilirubin (2× ULN)
3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening:
   - Moderate: CP-B (Scores 7 to 9) or
   - Severe: CP-C (Scores 10 to 12)
4. MELD score of 6 to 24 at Screening
5. Age ≥18 years
6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate or unresponsive to UDCA (no UDCA for ≥3 months)
7. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) with spermicide **or** (b) diaphragm with spermicide; or

- Intrauterine device; or
- Vasectomy (partner); or
- Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
- Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)

8. Must provide written informed consent and agree to comply with the study protocol.

8.3. Patient Exclusion Criteria

1. Non-cirrhotic or cirrhotic CP-A (Mild; Score 5 to 6)
2. History of liver transplant or organ transplant
3. History of alcohol or drug abuse within 12 months prior to Screening
4. Current hepatic encephalopathy (as defined by a West Haven score of ≥2 [AASLD, EASL 2014])
5. History or presence of other concomitant liver diseases including:
   a. Hepatitis C virus infection and RNA positive
   b. Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the Medical Monitor
   c. Primary sclerosing cholangitis
   d. Alcoholic liver disease
   e. Definite autoimmune liver disease or overlap hepatitis
   f. Gilbert's Syndrome
6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function prior to randomization
7. Patients with history or presence of hepatorenal or hepatopulmonary syndrome
8. Patients with significant active infection (ie spontaneous bacterial peritonitis)
9. Patients with known or suspected hepatocellular carcinoma
10. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
11. Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study
12. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
13. UDCA naïve (unless contraindicated)
14. Known history of human immunodeficiency virus infection

15. Treatment with commercially available fibrates or participation in a previous study involving fibrates within 3 months before Screening, or plans to use commercially available fibrates during the study
16. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating

8.4. Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study

Investigational product may be temporarily decreased (eg, from 10 mg twice weekly to 5 mg twice weekly, or from 5 mg twice weekly to 5 mg once weekly) or temporarily or permanently stopped based on tolerability concerns. Investigational product may be resumed at the maintenance dose upon resolution of gastroenteritis or worsening renal function or dehydration if there is no evidence of liver injury. For rechallenge following all other dose interruptions (see Table 5), investigational product should be initiated at a lower dose and patients monitored more frequently with up-titration considered based on tolerability.

Adjustments, interruptions, discontinuation, and any rechallenge of investigational product should be implemented per the criteria outlined in Table 5. Patients that discontinue investigational product are expected to continue in the study (and follow the regular visit schedule, with the exception of PK sampling [trough PK may be required in the event of an AE consistent with hepatic injury or decompensation]) until the end of the study, but may withdraw consent at any time.

Table 5: Criteria for Dose Adjustment, Interruption, Discontinuation, and Rechallenge

DOSE ADJUSTMENT		
Criteria	**Action Taken with IP**	**Adjustment**
New Onset Severe Pruritus	Drug holiday or less frequent dosing	Return to original dose regimen if tolerated
DOSE INTERRUPTION		
Criteria	**Action Taken with IP[a]**	**Rechallenge[b]**
If liver biochemistries indicative of suspected hepatic injury are identified as exceeding upper threshold criteria and require immediate interruption (see Part A of Table 3)[c]	Interrupt immediately upon initial observation	Patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.
Other liver biochemistries indicative of suspected hepatic injury are outside upper threshold criteria upon repeat testing as defined in Part A of Table 3[d]	Interrupt after confirmation by repeat testing	
Liver biochemistries indicative of potential hepatic decompensation in the absence of symptoms (see Part B of Table 3)[e]	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt	

Clinical events indicative of hepatic decompensation (see Part B of Table 4)	Closely monitor until normalization or stabilization	The patient may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator. IP should be re-initiated at a lower dose (or lower dose frequency) and titrated per Investigator discretion.
Gastroenteritis (established severe abdominal pain, vomiting, diarrhea for more than 4 days)	Interrupt	If no evidence of liver injury is detected, IP may be restarted at the same dose after resolution of intercurrent illness.
Evidence of worsening of renal function or dehydration	Interrupt	
DOSE DISCONTINUATION		
Criteria	**Action Taken with IP**	**Rechallenge**
If INR increases ≥2.0 in absence of clinical symptoms criteria (unless due to vitamin K deficiency) [f]	Discontinue / No Rechallenge	Discontinue IP permanently and continue to return for scheduled study visits for safety follow-up. Continue to return for scheduled study visits for safety follow-up. Monitor closely for clinical outcomes according to protocol assessments.
If total bilirubin thresholds (Part B of Table 3) are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy[f]		
Multi-Organ failure requiring hospitalization		
Liver transplantation		
Pregnancy		

Fully resolved = Return to baseline levels or return to within normal limits (WNL). IP = investigational product
[a] If patient is unable to be evaluated promptly, study drug must be immediately interrupted.
[b] Requires complete documentation of complete resolution or normal/baseline results based on laboratory parameters and symptoms.
[c] Total bilirubin baseline ≤ULN and ≥3x baseline, baseline >ULN and ≥2x baseline, ALT or AST >3x baseline (and >ULN)
[d] ALT or AST ≥2x baseline or electrolytes (sodium <130 mEq/L).
[e] Total bilirubin baseline ≤ULN and 1.5 mg/dL increase from baseline OR baseline >ULN and 1.0 mg/dL increase from baseline; INR >0.3 increase from baseline
[f] If INR increases ≥2.0 in the absence of clinical symptoms or if or total bilirubin thresholds OR an INR increase from baseline of ≥1.5 are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy.

8.4.1. Other Reasons for Discontinuation of Study or Investigational Product

The following events are considered appropriate reasons for a patient to discontinue investigational product; however, these patients are expected to continue in the study until study termination (or at the discretion of the Sponsor):

- Patient begins treatment with commercially available OCA.
- The Investigator or Sponsor considers that it is advisable or in the best interest of the patient.

- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to study drug.
- Withdrawal of consent
  - Consent may be fully withdrawn (in which case the patient discontinues both investigational product and study visits and procedures).
  - Consent may be modified to discontinue study visits but allow semi-annual telephone contact.
  - Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE) and liver-related clinical events.
  - Early termination procedures should be conducted if the patient withdraws consent (see Section 9.7.13).

The Investigator is encouraged to contact the Sponsor prior to discontinuing a patient from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any patient prematurely withdraws from the study.

8.4.1.1. Withdrawal of Consent to Continue in the Study

If the patient decides that it is in his/her best interest to discontinue from the study, he or she may withdraw consent. It is fully understood that all patients volunteer for the study and that they may withdraw their consent to continue in the study at any time.

Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.13).

A reasonable effort must be made to determine the reason(s) for patient discontinuation. This information and date must be recorded in the appropriate eCRF.

8.4.1.2. Lost to Follow-Up

Patients will be considered “lost to follow-up” only after documented attempts to reach the patient prove unsuccessful. A reasonable effort (ie, 2 phone calls/messages, no response to registered letter) must be made to contact the patient and determine the reason(s) why a patient fails to return for a study visit or is lost to follow-up. This information and date of contact must be recorded in the appropriate eCRF.

8.4.2. Patient Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. This information must be documented in the eCRF.

If a patient is withdrawn from the study early (regardless of the cause), all of the early termination (ET)/EOS evaluations are to be performed at the time of withdrawal, to the extent possible.

9. TREATMENT OF PATIENTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or placebo.

Two treatment groups will be evaluated: OCA and placebo. Investigational product will be administered orally. Each dose will be made up of 1 tablet (ie, one OCA 5 mg tablet or one OCA 10 mg tablet, or matching placebo).

Investigational product will be taken orally with water for the duration of the study. Patients will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time on dosing days. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.2) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications (including prescribed, over the-counter, or herbal preparations) taken within 30 days of Screening and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 1.

PBC Specific Therapy

Investigators will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. Throughout the course of the study, Investigators are expected to monitor patients' PBC regimens and, if responsible for usual care, may adjust the regimen to achieve locally-appropriate treatment goals. These goals will be individualized, with the understanding that currently applicable PBC guidelines may vary across different geographic regions.

Ideally, patients should generally remain on the baseline PBC therapies throughout the course of the study, unless the baseline PBC therapy is no longer considered clinically appropriate by the Investigator. In addition, patients should be reminded to keep taking their blinded investigational product.

9.2.1. Drug Interactions

Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should not be taken within 4 hours of taking investigational product (and UDCA if applicable), ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration.

OCA taken concomitantly with warfarin may result in decreased INR levels; therefore, INR should be monitored and the dosage of warfarin adjusted, as needed during treatment with OCA and after cessation of OCA, to maintain the target INR range.

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate probe, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

Information related to additional drug-drug interaction (DDI) studies is available in the current version of the IB. The aforementioned sections of the IB should be referred to during the course of the study, and are accessible to Investigators to help facilitate the assessment of potential DDIs with OCA that may be observed in study patients.

9.2.2. Prohibited Medications

Commercial OCA therapy (if available) is prohibited while on investigational product, and if prescribed during the course of the study, the Investigator should be cognizant of the possibility of double dosing. Patients who initiate with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.1). Fibric acid derivatives (ie, fibrates such as fenofibrate and bezafibrate) are also prohibited while on investigational product.

9.3. Treatment Compliance

The Investigator should assess the patient's compliance with dosing of investigational product at each study visit, and confirm by conducting investigational product accountability (ie, count of returned tablets).

Patients should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the indicated visits (Table 1). The Investigator or designee should perform investigational product accountability (ie, count of returned tablets) and, if applicable, follow-up with the patient to retrieve any investigational product bottles that have not been returned.

If the Investigator has concerns about a patient's dosing compliance, he or she should discuss this with the patient, assess the reasons for noncompliance and the likelihood that the patient will remain noncompliant, and notify the Sponsor accordingly.

9.4. Randomization and Blinding

9.4.1. Methods of Assigning Patients to Treatment Groups

This study will be conducted in a double-blind, placebo-controlled manner. Enrolled patients who meet all eligibility requirements will be randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or OCA based on a predefined randomization code (generated by Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based patient registration system at Screening and Day 1.

Randomization will be stratified by CP class (CP-B or CP-C). Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores. The IWRS will

serve as the investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the patient in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the patient to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind.

9.4.2. Blinding

The Sponsor, patients, Investigator, and study site staff will be blinded to the patient's treatment allocation during the patient's participation in the double-blind phase of the study.

9.4.3. Emergency Unblinding Procedures

Treatment assignment for individual patients will be made available to the Investigator for medical emergency use only (such as unblinding which is necessary in order to treat a serious adverse event [SAE] through the IWRS system). When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment assignment is necessary for further medical management of the patient). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the patient's record the rationale for unblinding and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment. Procedures for unblinding a patient's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual patient for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The DMC will have access to the IWRS and will be able to unblind individual patients. Refer to Section 15.8 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded patient data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the study is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DMC.

Access to treatment assignments will also be made available to the designated Intercept staff responsible for expedited safety reporting of suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

9.5. Assignment of Site and Patient Numbers

9.5.1. Site Numbers

Each study site selected to participate in this study will be assigned a site number by the Sponsor. The site number will be used to categorize patient data and to identify the site and/or Investigator within study documents. This number will be recorded in the eCRF.

9.5.2. Patient Numbers

Patients are assigned using a unique 10-character identifier (AAA-BBBCCC), independent of the randomization number. The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits represent the site number (BBB). The last 3 digits represent a unique screening number that is assigned in sequential order at each site starting with 001 (CCC).

9.6. Restrictions

Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited. Previous exposure to OCA (as a study participant or received commercial OCA therapy) is allowed provided patients haven't taken OCA within 3 months prior to enrollment in this study.

9.6.1. Fasting Requirement at Study Visits

All patients must have been fasting for at least 8 hours prior to their Screening Visit and all subsequent study visits, as all analytes will be assayed in fasting blood or plasma samples. Water is permitted during the fasting period.

9.7. Visit Procedures

9.7.1. Visit Windows

Visit windows are specified in the Schedule of Study Procedures (Table 1). Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. For example, Week 6 should ideally occur 6 calendar weeks (± 7 days) following Day 1.

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated informed consent form (ICF).

9.7.3. Assessing Cirrhosis

Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators:

- Biopsy results consistent with PBC Stage 4 (Ludwig 1978)

- Liver Stiffness as assessed by TE Value ≥16.9 kPa (Corpechot 2012)
- The presence of any of the following (unless exclusionary per Section 8.3) in the absence of acute liver failure:
  - Gastroesophageal varices
  - Ascites
  - Radiological evidence of cirrhosis (nodular liver or enlargement of portal vein and splenomegaly)
- Combined low platelet count (<140 000/mm^3) with:
  - Persistent decrease in serum albumin, or
  - Elevation in prothrombin time /INR (not due to antithrombotic agent use), or
  - Elevated bilirubin (2× ULN)

9.7.4. Screening Procedures (14 days to 28 days prior to Day 1)

Informed consent must be obtained from the patient before performing any study-related procedures, including Screening procedures. The Screening Visit assessments must be performed ≥14 days but less than 28 days prior to Day 1 to determine whether the patient meets all the inclusion criteria and none of the exclusion criteria. Patients who do not fulfill all eligibility criteria will not be enrolled in the study. Patients may be rescreened after 2 months have elapsed from the date of their most recent screening visit procedure; however, all Screening procedures (including obtaining informed consent) should be repeated and a new three-digit Screening number assigned.

Screening Visit procedures are as follows:

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Collect medical history.
- Collect PBC history.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination, including height, smoking and alcohol consumption history, and current habits for both.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.

- Perform a standard 12-lead electrocardiogram (ECG).
- Perform assessments for calculation of CP Score (Section 14.1.1)
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Virology Screen (HCV and HBsAg)
- Obtain urine sample for urinalysis
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test in females of childbearing potential.
- Instruct the patient to fast overnight (at least 8 hours) before the next visit (water is permitted).
- Record the visit in IWRS.
- Perform an ultrasound for HCC surveillance and evaluation of gallbladder status (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required. If the ultrasound cannot be performed at Screening (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed anytime within the screening visit window or on Day 1. Results from the screening ultrasound should be reviewed to assess possible exclusion criteria prior to randomization.

9.7.5. Day 1 Procedures (Randomization)

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.
- Review inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant heath care professional (HCP) or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).

- Administer Quality of Life and Patient questionnaires (Section 13.2.7).
- Randomize the patient only if s/he meets all inclusion criteria and no exclusion criteria.
- Record the visit in IWRS and dispense investigational product
  - Instruct the patient to begin dosing on the day of the Day 1 Visit.
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of fibrosis (ELF [HA, P3NP, and TIMP 1])
  - Fasting PK assessment
  - Bile Acid/C4/FGF-19
- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.
- If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.6. Week 3 and Week 42 Safety Visit Procedures

Preferably, the patient will come in to the clinic for this visit. Alternatively, the site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.

- Verify that patient is dosing as directed.
- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.

- Review and record prior concomitant medications.
- Assess and record AEs.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.
- **For Week 42 Only:** Assess for dose titration, if eligible. (Refer to Section 7.3)
- **For Week 42 Only:** Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
- Schedule the next visit (Week 6 or Week 48), reiterate dosing instructions, and advise the patient:

  For Week 3 Only:

  - **Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose**, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3).
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

  For Week 42 Only:

  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.7. Week 6 Procedures

Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3).

- Verify that the patient has fasted for at least 8 hours.

  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Bile Acids/C4/FGF-19
  - Fasting PK assessment
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.8. Week 9 through Week 48 (Safety Contact)

Patients should be contacted by telephone/email at Week 9 and every 3 weeks afterward to Week 48.

- Contact patient by phone/email.
- Review and record prior concomitant medications.
- Assess and record AEs.

- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess investigational product compliance, perform investigational product accountability.

9.7.9. Week 12, Week 24, Week 36 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Perform a physical examination.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible. (Refer to Section 7.3)
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Markers of fibrosis (ELF [HA, P3NP, and TIMP 1])
  - Bile Acid/C4/FGF-19
  - Fasting PK assessment (**Week 36 only**)

- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit.
- Perform an ultrasound for HCC surveillance at **Week 24 ONLY** (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Serial PK assessment **at Week 12 and 24 ONLY (not done at Week 36)**; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose

Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.

- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to visits; s/he will dose at the clinic for Week 18 and Week 30 visits (if this is in compliance with the established dosing frequency), and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.10. Week 18 and Week 30 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF.
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination.

- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Bile Acid/C4/FGF-19
- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose

Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.

- Schedule the next visit, reiterate dosing instructions, and advise the patient:

- NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s) to both visits; s/he will dose at the clinic on Week 24 (if this is in compliance with the established dosing frequency), and
- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.11. Week 48 Procedures

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.
- Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform ECG.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform urinalysis
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation

- Markers of fibrosis (ELF [HA, P3NP, and TIMP 1])
- Bile Acids/C4/FGF-19

- Serial PK assessment; the following procedures will be conducted in all patients:
  - 30 minutes prior to dosing: collect predose blood sample
  - Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water.
  - Collect blood samples at: 30 min, 45 min, 1 hour postdose
  - Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose

Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.

- Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data are needed for cirrhosis assessment) or as close as possible to the visit.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit, and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

9.7.12. Every 3 Months after Week 48

Quarterly

- Verify that the patient has fasted for at least 8 hours.
  - Record fasting status in the source and eCRF
  - If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.

- Perform a physical examination, including height, smoking and alcohol consumption history, and current habits for both.
- Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.
- Assess and record vital signs and weight (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- Perform assessments for calculation of CP Score (Section 14.1.1).
- Administer Quality of Life and Patient questionnaires (see Section 13.2.7).
- Assess investigational product compliance, perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.3).
- Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
- Schedule the next visit, reiterate dosing instructions, and advise the patient:
  - NOT to take investigational product on the morning of the next visit, and
  - To bring the investigational product bottle(s) to the visit, and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.

Patients will complete a TE/ELF (HA, P3NP and TIMP 1) and ultrasound (for HCC surveillance) assessment, every 6 months (±2 weeks) after Week 48.

ECG and urinalysis will be done yearly (±2 weeks) after Week 48.

9.7.13. End of Study/Early Termination/End of Treatment Procedures for Patients That Withdraw from Investigational Product or Withdraw Consent

Patients who discontinue investigational product before Week 48 are expected to continue in the study until the end of the study (EOS [when patient terminates the study]) or at the discretion of the Sponsor.

EOT (when patient discontinues investigational product)/ET procedures will be required whenever patients discontinue treatment with investigational product (Table 1, Section 9.7.11). The EOT/ET Visit (Table 1) and procedures listed below (Table 6) must be performed as close as possible to the patient's last dose of investigational product. When a patient discontinues or interrupts investigational product and continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. The actual investigational product discontinuation scenario (Table 6) will determine the sequence of the EOT/ET and EOS Visits and procedures. In some cases, the EOT/ET Visit and procedures will precede the EOS Visit; in others, the EOT/ET and EOS Visits will be combined and performed as close as possible to the patient's last dose of investigational product. EOT and EOS Visits are encouraged but at no time will a missed EOT or EOS visit be considered a protocol deviation.

When a patient ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (ET) (withdrawal of consent) or discontinuation, an EOT/EOS Visit must be performed as near as possible to her/his last dose of investigational product and the procedures listed in Table 1 performed. The purpose of this visit is to conduct complete and/or final assessments on or as near as possible to the final day of dosing. In some cases, the patient may discontinue on the day of a scheduled study visit. In these cases, EOT/EOS Visit procedures should be performed in place of the scheduled study visit procedures. The data will be recorded as EOT/ET and EOS procedures in the eCRF.

Table 6: Early Discontinuation Scenarios

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Early Termination	Discontinued	Withdrawn	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product.	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose of investigational product.	Complete at final study visit.
	Discontinued	Record review only	Record review only	Combined visit, completed as close as possible to last dose of investigational product.	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product.	
Pregnancy	Discontinued	Complete per the above scenarios - Early Termination or Treatment Discontinuation			
Lost to Follow-Up	Discontinued	LTF	None	Unable to complete due to LTF status	

EOS = end of study; EOT = end of treatment; LTF = lost to follow-up

[a] Refer to Section 7.1.2, Schedule of Study Procedures for all procedures and evaluations required at the EOS and EOT Visits.

[b] Includes initiation of commercially available OCA.

9.7.14. Unscheduled Safety Visit

The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted.

As appropriate, the Medical Monitor should be contacted.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

The investigational product is a white, round, film coated tablet containing OCA 5 mg or 10 mg or matching placebo. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

10.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to Good Manufacturing Practice standards by a designated qualified vendor. All investigational product will be provided as tablets for oral administration and provided in high density polyethylene bottles with heat induction seals and child resistant closures. The bottle packaging will not reveal any information about the treatment dose contained in the bottle. Multiple bottles may be dispensed to the patient at each visit to provide enough tablets for dosing until the next visit.

The designated investigational product packaging/distribution vendor will also be responsible for the distribution of the investigational product to the Investigator.

10.3. Investigational Product Storage

All OCA tablet strengths provided to clinical study sites in support of clinical studies are to be shipped and stored at 15°C to 25°C. Temperature excursions within the range of 2°C and 30°C for no more than a 6-month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20°C to 40°C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.

10.4. Investigational Product Administration

Refer to Section 9.1.

10.5. Investigational Product Accountability and Disposal

The Sponsor's representative will send investigational product to the study site under appropriate storage conditions. All shipments of investigational product should be unpacked and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of

the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product against the shipment documentation. The pharmacist or designee should contact the Sponsor immediately to report any concerns regarding the shipment.

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of investigational product accountability, including records of individual patient dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the Clinical Research Associate (CRA), will review accountability records against investigational product dispensed and that remaining in stock, during on site monitoring visits and when the study is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the investigational product. If the investigational product is to be returned to the Sponsor's vendor for destruction, the CRA will also prepare the investigational product for shipment.

11. OVERVIEW OF ASSESSMENTS

The assessments supporting the objectives for the study are in Table 7:

Table 7: Table of Assessments

Primary Objectives	**Assessments**
PK parameters	OCA and its conjugates glyco-OCA and tauro-OCA, and metabolite OCA glucuronide
Safety and tolerability	SAEs and TEAEs, physical exam, ECG, vital signs, clinical laboratory assessments, discontinuations, pruritus, and fatigue
Secondary Objectives	**Assessments**
Changes in risk scores	Changes in MELD and in CP Scores and components of the CP score and MELD score
Changes in liver biochemistry and hepatobiliary damage	Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets
PD parameters	FGF-19, C4, and plasma bile acids
Additional Objectives	**Assessments**
Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis	TE/ELF (HA, P3NP, and TIMP-1)
PK/PD relationship	PK parameters compared to PD parameters and safety and tolerability assessments (above)
Patient-reported outcomes	Pruritus VAS, PBC-40, EQ-5D-5L, CLDQ
Clinical events	Death (all-cause and liver-related), liver transplant, MELD score ≥15 (for patients with MELD ≤12 at baseline), hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and HCC.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C4 = 7α-hydroxy-4-cholesten-3-one; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; INR = international normalized ratio; MELD = Model End Stage Liver Disease; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PBC = Primary Biliary Cholangitis; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TE = Transient Elastography; TEAE = treatment emergent adverse events; TIMP-1 = tissue inhibitor of metalloproteinase 1; VAS = visual analog scale

12. CLINICAL PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic analyses will be based on the PK population (Section 15.1). Patients in the PK Population with at least one PD assessment after dosing will be included in the combined PK/PD analyses.

12.1. Pharmacokinetic Blood Sampling

Serial and fasting PK assessments will be performed in all patients participating in the study.

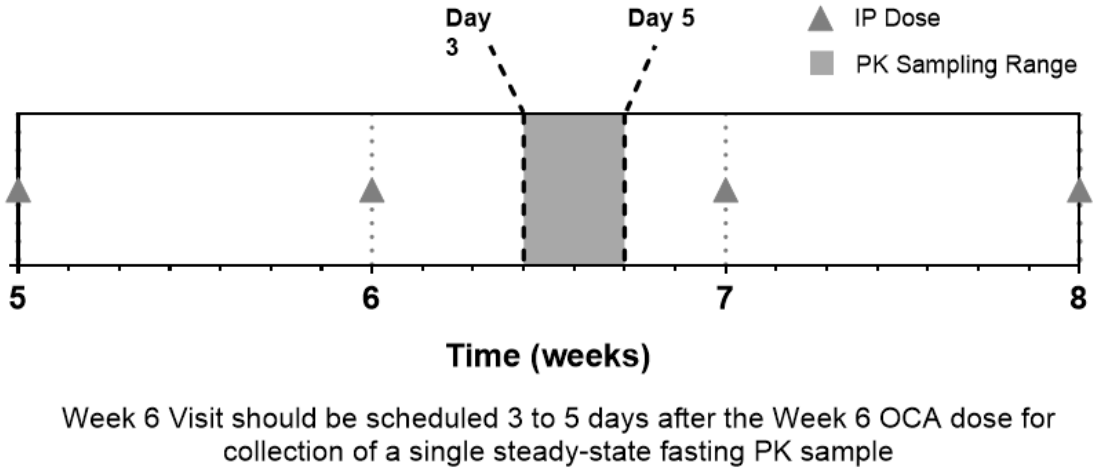
At Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48, patients will provide fasted blood samples for measurement of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide 30 minutes before administration of investigational product (Table 8). Patients will then receive a dose of investigational product with approximately 240 mL of water.

Week 6 Visit should occur 3, 4, or 5 days **after** the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure 3]).

During the treatment period:

- Pharmacokinetic fasting samples will be obtained from all patients at Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48 prior to dose administration in accordance with Figure 4.
- Serial PK assessments will be performed in all patients at Weeks 12, 18, 24, 30, and 48.

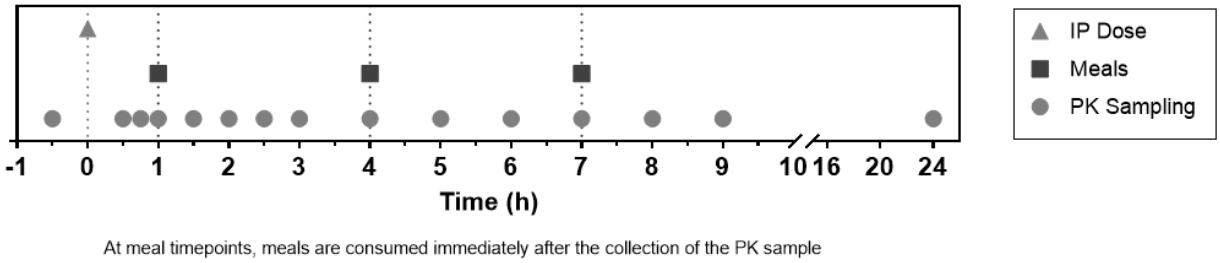
Figure 3: Week 6 Sampling Schedule



IP = investigational product; PK = pharmacokinetic

At Weeks 12, 18, 24, 30, and 48, serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose (Figure 4) for all patients. The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. The home health care agency must be advised one week in advance of the appointment.

Figure 4: Pharmacokinetic Sampling Schedule



h = hour; IP = investigational product; PK = pharmacokinetic

Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. The nutritional information of the meal replacement drink should be submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection.

Table 8: Acceptable Windows for Pharmacokinetic Sample Collection

Nominal Sampling Time	Acceptable Sampling Window
Before administration of investigational product (predose or fasting)	Within 30 minutes before dosing
0.5 to 1.5 hours after investigational product	± 10 minutes
2 to 2.5 hours after investigational product	± 20 minutes
3 to 24 hours after investigational product	± 30 minutes

12.2. Processing and Handling of Pharmacokinetic Samples

Whole blood will be collected at each scheduled sample timepoint. Detailed procedures for the collection of blood samples including further processing into plasma will be provided in a separate laboratory manual. The storage and shipment procedures for subsequent bioanalysis, will be provided to the investigational site and home health care company in a separate document before the study is initiated.

12.3. Bioanalysis

Plasma concentrations of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide will be determined using a validated liquid-chromatography mass spectrometry/mass spectrometry (LC/MS/MS) method. A detailed description of validation information and results from the bioanalytical assay will be provided in separate reports. These samples may be used for evaluation of metabolites of OCA or other concomitant medication, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by OCA.

13. ASSESSMENT OF SAFETY

13.1. Adverse Events and Serious Adverse Events

13.1.1. Definitions of Adverse Events

13.1.1.1. Adverse Event

AEs are defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to investigational product. An AE, also referred to as an adverse experience, can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) patient deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE.

Patients should be questioned about AEs in a general way, without leading the patient or asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

Patients should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as: pale-colored stools, urine color from pale to deep amber [dark], nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or the whites of eyes, and bruising easily.

13.1.1.2. Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

13.1.1.3. Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

13.1.1.4. Adverse Events of Special Interest

The following decompensation events are adverse events of special interest; a subset of these are also captured as additional efficacy assessments (see Section 14.2.3).

- Variceal bleeding or recurrent variceal bleeding documented by endoscopy OR patient presenting with anemia or melena (hemoglobin drop ≥2 g/dL) and found to

have varices documented by endoscopy, irrespective of hospitalization or requirement of blood transfusion.

- Gastrointestinal bleeding as a result of gastric or duodenal varices verified by endoscopy
- Hepatic encephalopathy, Grade ≥2
- New onset ascites requiring treatment
- Worsening of ascites (requiring increase in drug therapy or requirement of surgical procedure such as paracentesis or shunt placement)
- Refractory ascites -unresponsive to medications, and patient is not a candidate for TIPS or shunt and requires large volume paracentesis
- Hyponatremia (Na ≤125 mEq/L) secondary to ascites
- Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis- by cell count/chemistry)
- Hepatorenal syndrome Type 1 and Type 2 and Acute Kidney Injury (AKI)
- Liver failure defined as worsening of liver synthetic function that is persistently worse relative to baseline and/or progressive over time:
  - Hepato-pulmonary syndrome
  - Porto-pulmonary syndrome
  - Liver Transplant
  - Increase in MELD scores by 3 points relative to baseline, persistent over time and unrelated to vitamin K deficiency related increase in INR
  - Any liver related event that requires hospitalization and treatment

13.1.2. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 9. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as suspected adverse reaction (SAR). "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "definite," "probable," or "possible" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 9: Relationship of Adverse Events to Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; that is confirmed by stopping or reducing the dosage of the investigational product; and that could not be reasonably explained by the known characteristics of the patient's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product; that does not follow a known or suspected response pattern to the suspected investigational product; and that could reasonably be explained by known characteristics of the patient's clinical state.
Not Related	Any event that does not meet the above criteria.

13.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 10, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 10: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Causing no limitation of usual activities; the patient may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the patient may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.

13.1.4. Reporting of Adverse Events and Serious Adverse Events

13.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the patient fully completes her/his study participation.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for

duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any patient.

13.1.4.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

All SAEs must be reported to the Sponsor (including suspected liver-related clinical outcome events that qualify as serious). SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by:

- E-mail to the SAE email address: PPD
- Fax using a paper SAE report form: PPD

If an SAE is reported by fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Patient number
- Event term
- At least 1 criterion classifying the event as serious
- Name and title of the reporting individual
- Causal relationship to the investigational product

The Investigator will assess whether the event is causally related to the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of Safety Reports/Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to PPD or emailed to PPD as soon as possible.

The Investigator is responsible for submitting information on Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local country requirements. Documentation of the submissions to IRBs/IEC s must be retained in the appropriate study file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate investigative site study files or with the IB.

13.1.5. Additional Investigator Responsibilities for SAEs

The safety data recorded in the EDC represent the official record of all AEs and SAEs reported in the study. The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the patient's AE eCRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Sponsor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for patient care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the Medical Monitor.

13.1.6. Notification of Post-Treatment SAEs for Patients Who Continue in the Study

Post-treatment SAEs that occur in patients who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2 .

SAEs that occur in patients who discontinue investigational product, initiate treatment with commercially available Ocaliva, and remain in the study must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

13.1.7. Notification of Post-Study SAEs

All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2.

13.1.8. Follow-Up of AEs and SAEs

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

Drug-Induced Liver Injury or Disease Progression

All patients showing possible drug-induced liver injury or disease progression should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should

be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

Cholecystitis or Pancreatitis

Patients should be instructed to contact the investigational site if they experience any of the following signs and symptoms: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, or weakness. Patients should also be counseled to seek immediate medical assistance if they experience persistent severe abdominal pain.

In the event that cholecystitis and/or pancreatitis is suspected, Investigators should promptly bring patients into the clinic to undergo a complete evaluation, including a physical examination, and laboratory assessments [ie, amylase and lipase]). Investigators should refer to standard of care guidelines on suspected pancreatitis (Banks 2012, Greenburg 2015). Diagnosis of acute pancreatitis includes 2 of the following:

- Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (or amylase) at least 3 times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging

To ensure appropriate vigilance, amylase and lipase levels should be monitored monthly for 3 months after onset of symptoms, irrespective of whether a diagnosis of cholecystitis and or pancreatitis is confirmed. The Investigator should contact the Medical Monitor upon awareness of the above (ie, suspected or confirmed diagnosis). Results should be recorded promptly in the eCRF.

13.1.9. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when and AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 13.1.4 must also be followed.

13.2. Other Safety Parameters

13.2.1. Medical History/Demographics

A complete medical history will be obtained from the patient at screening. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

13.2.2. Medical and Surgical Procedures

Medical and surgical procedures will be recorded at the visits indicated in Table 1.

13.2.3. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the visits specified in the Schedule of Study Procedures (Table 1). A basic physical examination should be performed, including all body systems pertinent to the patient. Smoking and alcohol consumption history and current habits will be recorded. Any clinically significant abnormality should be reported on the AE eCRF page for findings that appear after consent, and on the medical history eCRF for any finding present prior to consent.

13.2.4. Vital Signs and Weight

Vital signs (oral temperature, sitting heart rate, respiratory rate and sitting blood pressure [BP]) and weight will be assessed at indicated visits (Table 1). When taking heart rate, respiratory rate and BP readings, patients should be seated quietly for a minimum of 3 minutes before the readings are taken.

13.2.5. Electrocardiogram

Standard ECGs will be collected at indicated visits (Table 1). The Investigator or designee will review the ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after Day 1 will also be documented as AEs and entered on the AE page of the eCRF.

Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time.

13.2.6. Laboratory Assessments

Patients will be instructed to attend each study visit in a fasted state, preferably in the morning, and patients should remain fasted until their blood samples have been collected. At all visits, the Investigator or designee will verify that the patient has fasted for at least 8 hours and record fasting status in the source and eCRF. If the patient reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and eCRF and remind the patient that fasting is required before all study visits.

Blood samples for serum chemistry, coagulation, and hematology; and urine samples will be collected at visits as detailed in the Schedule of Study Procedures (see Table 1). The number and volume of samples to be collected at each visit will be detailed in the laboratory manual.

Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

All patients with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.

Laboratory samples will be stored for a maximum of up to 1 year after the end of the study (depending on stability) in the event that retesting is required, and destroyed after 1 year if not analyzed.

The list of laboratory analytes to be tested is shown in Table 11.

Table 11: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen, creatinine, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, total bilirubin, free fatty acids, TFT (TSH, free T3 and free T4)
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)
Coagulation	PT, PTT, INR
Urinalysis; Pregnancy	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, leucocytes, nitrates; albumin, creatinine, albumin/creatinine ratio (if positive); β-hCG
Markers of Cholecystitis and Pancreatitis	Amylase and lipase
Noninvasive measurements of liver fibrosis	ELF (HA, P3NP, and TIMP-1)
PK assessments	OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)
PD markers	C4, FGF-19 and plasma bile acids

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = human chorionic gonadotropin; C4 = 7α-hydroxy-4-cholesten-3-one; CPK = creatine phosphokinase; ELF = enhanced liver fibrosis; FGF-19 = fibroblast growth factor-19; GGT = gamma-glutamyl transferase; HA = hyaluronic acid; HDL = high density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; OCA = obeticholic acid; P3NP = procollagen 3 N-terminal peptide; PT = Prothrombin time; PTT = partial thromboplastin time; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TG = triglyceride; TFT = thyroid function test; TIMP-1 = tissue inhibitor of metalloproteinase 1; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein

Laboratory reference ranges for the study will be based on the laboratory vendor range.

Urine based β-hCG pregnancy tests will be performed in female patients of childbearing potential per protocol specified visits (see Table 1). If a urine pregnancy test is positive, a serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified and the patient will be followed as outlined in Section 13.1.9 until pregnancy outcome.

INR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, and INR values, with modification by United Network for Organ Sharing. Total OCA will be calculated based on the sum of OCA, glycol-OCA, and tauro-OCA concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.

13.2.7. Patient-Reported Outcomes and Healthcare Resource Use

Data will be collected to determine the effects of OCA on health-related quality of life. Healthcare resource use as well as a general health status assessment (for the purposes of generating health utilities) will be used to support subsequent cost-effectiveness analyses that are relevant to major health care systems around the world. Assessments of patient-reported outcomes will take place during the visits indicated in Table 1.

The following patient-reported outcomes will be used to evaluate the effects of OCA compared to placebo on improvements in health-related quality of life:

- PBC-40: The PBC-40 is a validated disease-specific 40-question quality of life questionnaire, which consists of 6 domains: General Symptoms, Itch, Fatigue, Cognitive Function, Social, and Emotional (Jacoby 2005).
- EQ-5D-5L: The EQ-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VASs). The descriptive system is organized into 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the patient's self-rated health on a 20-cm vertical, line with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman 2011, Oemar 2013).
- Pruritus VAS: A VAS will also be used to assess pruritus in individual patients.
- Chronic Liver Disease Questionnaire: The CLDQ is a disease-specific health related quality of life questionnaire for patients with chronic liver disease. The questionnaire includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry). Each question is answered on a scale from 1 (always) to 7 (never) with a higher score corresponding to a better quality of life. The CLDQ produces a summary score and domain scores that correlate with the severity of liver disease (Younossi 1999).

Patients will be asked to complete the questionnaires and initial and date each document. The questionnaires should be filed in the patient's study records. These may require transcription to the eCRF by study site staff.

Healthcare resource use will be collected from eCRFs including number, reason for and duration of hospitalizations and emergency room visits, number of outpatient physician visits (patient reported), and use of concomitant medications. The purpose is to evaluate the effects of OCA compared to placebo on patient-reported outcomes and healthcare resource.

14. EFFICACY ASSESSMENTS

14.1. Biochemical Measures of Disease Severity

14.1.1. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory.

Table 12: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	µmol/L	<34	34-50	>50
	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	28-35	<28
	g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Mild	Moderate-Severe
Hepatic encephalopathy[a]		0	Grade 1 or 2	Grade 3 or 4

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
(Pugh 1973, Lucey 1997), Vilstrup 2014

14.1.2. Model of End Stage Liver Disease Score

The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is useful in assessing patients with significant decompensation, and the MELD score is now used by the United Network for Organ Sharing in the US and Eurotransplants to manage the organ allocation for liver transplantation. The threshold for placement on an organ transplantation queue varies between regions across the globe.

An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival (Kamath 2007). MELD score will be calculated and reported for visits where these parameters are measured (see Table 1).

14.1.3. Changes in Liver Biochemistry and Hepatobiliary Damage

ALP, ALT, AST, GGT, total and direct bilirubin, INR, creatinine, albumin, platelets will be measured according to the frequency listed in Table 1.

14.2. Additional Assessments

14.2.1. Noninvasive Measurements of Liver Stiffness and Fibrosis

The ELF test assesses: HA, P3NP, and TIMP-1. Samples will be assessed in patients according to the schedules presented in Table 1.

The Fibroscan® TE device (Echosens, Paris, France) will be used at all study sites that have the equipment to collect hepatic stiffness measurements. These study sites must have the staff trained in the use and data interpretation of the device. This is a validated and non-invasive radiological technique used to assess hepatic fibrosis which will be conducted according to the schedule presented in Table 1.

14.2.2. Markers of FXR activation

Blood samples will be collected in all patients to measure C4, FGF-19, and bile acids. The results of these analyses will be used to assess the PK/PD response of OCA. Blood samples will be assessed in patients according to the schedule presented in Table 1.

14.2.3. Clinical Outcome Events

Clinical outcome events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.

15. STATISTICAL METHODS AND ANALYSES

Individual patient data obtained from electronic case report forms (eCRFs), central laboratories, external sources, and any derived data will be presented in data listings by patient. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on treatment study days are numbered relative to the day of the first dose of investigational product which is designated as Day 1.

All output will be incorporated into Microsoft Word rich text format (.rtf) files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, Baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For continuous variables, the number of patients, mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more decimal place than the raw data, and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate. Confidence intervals (CIs) will be provided and will be rounded to 1 decimal place, unless otherwise specified.

Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations.

There will be no formal hypothesis testing in this study. However, summary statistics for each treatment group will be presented, as well as 95% CIs for the difference between the treatment groups.

15.1. Analysis Populations

The following patient populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized patients who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy assessments.
- The Safety Population will include all patients who received at least one dose of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses.
- The PK population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

15.2. Determination of Sample Size

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. A total of 30 patients is adequate with 10 patients on placebo to be included as a comparator and 20 patients on OCA. An additional

20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized in a 1:1 ratio to 1 of the 2 treatment groups: Placebo and OCA.

15.3. Pharmacokinetic Analyses

The PK Population will be used for analysis of PK parameters, which include plasma OCA (parent) and its conjugates (glyco-OCA and tauro-OCA), total OCA, metabolite OCA glucuronide, and potentially other conjugates or metabolites not yet identified.

PK analysis will be based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics. Full details regarding the planned analyses, methods, and outputs for the study will be detailed in the statistical analysis plan (SAP).

15.4. Safety Analyses

Safety analyses will be conducted using the Safety population. Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vital signs, ECG, and clinical laboratory results will be summarized by treatment group using the Safety Population.

The incidence of TEAEs and SAEs will be tabulated by system organ class (SOC) and preferred term (PT) for each treatment group, and similarly by severity and relationship to treatment.

Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized.

No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.

15.4.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided.

Each AE summary will be displayed by treatment group. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs.
- Patient incidence of TEAEs and the total number of entries by MedDRA SOC and PT. This summary will be repeated for all subgroups.
- Patient incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Patient incidence of TEAEs by MedDRA SOC, PT, and closest relationship to investigational product (Related/Not Related). Related AEs are those with relationships reported as “Definite,” “Probable,” or “Possible,” and unrelated AEs are

those with relationships reported as "Unlikely" or "Not Related." At each level of patient summarization, a patient is classified according to the closest relationship if the patient reported 1 or more events. AEs with a missing relationship will be considered related for this summary.

- Patient incidence of serious TEAEs and the total number of entries by MedDRA SOC and PT.
- Patient incidence of TEAEs leading to investigational product withdrawal or study discontinuation by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Patient Discontinued from Study" is checked.

The following listings will be presented by treatment group and patient:

- All adverse events.
- Serious adverse events (This is a subset of the AEs where serious is marked as "Yes").
- Severe adverse events (This is a subset of AEs where severity is marked as "Severe").
- Related adverse events (This is a subset of the AEs where relationship marked as "Definite," "Probable," or "Possible").
- Adverse events leading to Study Drug Withdrawal or Study Discontinuation (This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Patient Discontinued from Study" is checked).
- Adverse events leading to death (This is a subset of the AEs where the corresponding AE number is specified on the Death eCRF).

Adverse events of special interest as defined in Section 13.1.1.4 will be summarized for each treatment group.

15.4.2. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment.

In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.

15.4.3. Additional Safety Analysis

Vital Signs and Weight

The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.

Electrocardiograms

Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.

15.4.4. Adverse Events of Special Interest

Pruritus: Treatment-emergent pruritus, defined as any PT including "Prur," will be summarized separately by the MedDRA SOC, treatment group, and PT as a subset of all TEAEs. This summary will be repeated for patients with "new or worsened" pruritus events, as defined as follows:

- Mild, moderate, or severe treatment-emergent pruritus events in patients with no pruritus at Baseline, or
- Worsening of the severity of the Baseline condition in patients with pruritus at Baseline.

Baseline pruritus is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose Baseline severity is severe will be counted as worsening if an AE of pruritus with severe is recorded.

An analysis of treatment-emergent pruritus event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between pruritus and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent pruritus
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Patients who never reported an AE of pruritus will be censored at the date of last contact.
- Time to onset of the first moderate or severe treatment-emergent pruritus
  - The time to the start of the first moderate or severe pruritus will be calculated by date of onset of the first moderate or severe pruritus – date of first dose of investigational product +1.

  - Patients who never reported a moderate or severe AE of pruritus will be censored at the date of completion or discontinuation.
- Time to onset of the first severe treatment-emergent pruritus
  - The time to the start of the first severe pruritus will be calculated by date of onset of the first severe pruritus – date of first dose of investigational product +1.
  - Patients who never reported a severe AE of pruritus will be censored at the date of completion or discontinuation.

The analysis of time to first onset of treatment-emergent pruritus AE, time to onset of the first moderate or severe treatment-emergent pruritus, and onset of the first severe treatment-emergent pruritus will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without pruritus (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The tabulation will include the KM estimate methodology using 25th, 50th (median), and 75th percentiles of the medians and corresponding with associated 2-sided 95% confidence intervals (CIs), if the medians can be estimated as well as percentage of censored observations.

Fatigue: Treatment-emergent fatigue is defined as any PT which includes "Fatigue." New or worsened treatment-emergent fatigue is defined as follows:

- Any mild, moderate, or severe treatment-emergent fatigue events in patients with no fatigue at Baseline, or
- Worsening of the severity of the Baseline condition in patients with fatigue at Baseline.

Baseline fatigue is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose Baseline severity is severe will be counted as worsening if an AE of fatigue with severe is recorded.

An analysis of treatment-emergent fatigue event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized. Each individual patient year on study will be derived as the last known date during the study minus the first dose date plus 1 divided by 365.25 days/year.

In order to explore the relationship between fatigue and the investigational product, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent fatigue
  - The time to the start of the first episode will be calculated by date of onset of first episode – date of first dose of investigational product + 1.
  - Patients who never reported an AE of fatigue will be censored at the date of last contact.
- Time to onset of the first moderate or severe treatment-emergent fatigue

  - The time to the start of the first moderate or severe fatigue will be calculated by date of onset of the first moderate or severe fatigue – date of first dose of investigational product +1.
  - Patients who never reported a moderate or severe AE of fatigue will be censored at the date of last contact.
- Time to onset of the first severe treatment-emergent fatigue
  - The time to the start of the first severe fatigue will be calculated by date of onset of the first severe fatigue – date of first dose of investigational product +1.
  - Patients who never reported a severe AE of fatigue will be censored at the data of last contact.

The analysis of time to first onset of treatment-emergent fatigue AE, time to onset of the first moderate or severe treatment-emergent fatigue, and onset of the first severe treatment-emergent fatigue will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without fatigue (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group.

15.5. Efficacy Analyses

This study does not plan to test a formal hypothesis for any efficacy endpoint.

The endpoints of efficacy assessments are change in total and direct bilirubin, INR, creatinine, albumin, platelets, ALP, ALT, AST, and GGT from baseline to Week 48 (end of the study), change from baseline to Week 48 in CP score and components of the CP score, and change from baseline to Week 48 in MELD and components of the MELD score. Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Analyses of change from Baseline to Week 48 (end of study) will be modelled between treatment groups using ANCOVA model with change from Baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Summary statistics of the laboratory values will be provided by treatment group. The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 2-sided 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 2-sided 95% CI of the difference will also be presented.

Risk Scores: Changes from baseline in the MELD score and in CP score, C4, FGF-19 and plasma bile acids will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be

constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.

Shifts in MELD scores from Baseline will be reported by visit using the following categories: <10, 10 to <12, 12 to <13, 13 to <14, 14 to <15, and ≥15.

CP class will be presented in shift tables showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of patients within each shift classification.

Individual factors will be presented in a listing.

15.6. Additional Efficacy Analyses

Analyses of changes in liver stiffness (TE) and liver fibrosis (ELF [HA, P3NP, and TIMP-1]) will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin.

The following clinical endpoints will be captured in the study:

- Time to death (all cause)
- Time to liver-related death
- Time to liver transplant
- MELD score ≥15 (for patients with MELD ≤12 at baseline)
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Time to variceal bleed
  - Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC) will be summarized by treatment group using the same methods as defined above.

Full details regarding additional efficacy analyses will be detailed in the SAP.

15.7. Handling of Missing Data

Missing data will be assumed to be missing at random. No data will be imputed.

15.8. Data Monitoring Committee

An independent DMC includes hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), and statistician(s) not involved in the study as Investigators, adjudication committee members, or consultants. The DMC will have oversight of the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the Food and Drug Administration (FDA) debarment list will not be offered membership. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data in order to ensure the safe and proper treatment of patients. Based on review of these data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study.

Written minutes of both the open and closed DMC sessions will be prepared. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked.

Data listings provided to the DMC do not contain individual patient treatment information; however, the DMC will have access to the database and may unblind individual patient data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all patients and separate treatment columns with 'dummy' labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.

The DMC may agree to adjust meeting frequency based upon actual and projected safety and efficacy data availability. Adjustments to or stopping of the protocol defined doses may be considered based on DMC evaluation of OCA safety and tolerability.

All Investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to patient safety, which alter the conduct of this study. The Investigators will inform the patients of such actions and the protocol, PIS, and ICF will be revised, as appropriate.

15.9. Adjudication Committees

All suspected liver-related clinical events, major adverse cardiovascular events (MACE)/expanded MACE, and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 3 committees and event types they are responsible for adjudicating are as follows:

- Cardiovascular Adjudication Committee (CAC): Adjudicates all suspected MACE, including all deaths
- Hepatic Outcomes Committee: Adjudicates all deaths and suspected liver-related outcomes
- Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events

Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the suspected events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual patient treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. Study Monitoring

Study records at each site will be monitored at regular intervals by a representative of the Sponsor, the CRA. The role of the CRA is to aid the Investigator in the maintenance and documentation of complete, accurate, legible, well organized and easily retrievable data. In addition, the CRA will ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such must be given access to the patient’s primary source documentation (eg, paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

The Investigator may exercise judgment in allowing the CRA access to particular sections of the patient's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

16.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IEC/IRB, and/or regulatory agencies to conduct one or more site audits during or after the study and agrees to allow access to all study-related documentation and information and be available for discussion about the study.

17. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the Sponsor or designated personnel (eg, CRA), instruction manuals, data verification, cross checking, and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate collection of study data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

18. ETHICS

18.1. Ethics Review

The final study protocol, including the final version of the PIS-ICF and/or other patient information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to Intercept before he or she can enroll any patient into the study. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to study patients to the IRB/IEC for review.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. A favorable opinion on amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/ IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of SARs will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or its designee will provide reports to the IRB/IEC as requested, as a minimum annually, and after the study is complete.

18.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, "(64th World Medical Association [WMA] General Assembly, Fortaleza, Brazil, October 2013),"and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

18.3. Written Informed Consent

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated consent form must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the patient.

18.4. Patient Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification but the patient's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

The Investigator will maintain a list of patient's names and identifying information (eg, patient's hospital number, unique patient number). This list will not be collected by the Sponsor.

The PIS-ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique patient number/randomization code/site number, only.

When personal data on patients are stored or processed by computer, the data must be protected to prevent disclosure to unauthorized third parties. The pertinent sections of the data protection laws in the country in which the protocol is being conducted will be complied with in full.

The PIS-ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, regulatory authorities, or IEC/IRBs may require direct access to parts of the hospital or study site records relevant to the study, including patient's medical history.

19. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the patients for the duration of the study. If the Investigator is not present in the study site during the assessment, he or she will leave instructions for the study site staff and a telephone number where he or she can be reached.

Named physician(s) will be responsible for the medical follow-up of patients, as applicable.

19.1. Adverse Event Reporting

The Investigator is responsible for recording AEs reported by the patient or discovered by any other means during the study. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

19.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the Investigator considers a patient's safety to be compromised if immediate action is not taken.

19.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

- Approved PIS-ICF (all versions)
- IRB/IEC approvals (of protocol/amendments, patient questionnaires, etc)
- Form FDA 1572
- Current medical license of Investigators
- Curriculum vitae of Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

19.4. Ethics Review (IRB/IEC)

Please see Section 18.1 for the Investigator's responsibilities regarding ethics review.

19.5. Archiving and Record Retention

The Investigator should retain all essential documents and correspondence relating to this study in the Investigator Site File (ISF). Any study documents stored elsewhere should have their location referenced in the ISF table of contents or in a note to file.

All documents relating to the study including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed study patient log and

confidential patient identification list will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor before the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

20. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include the following:

- Clinical Trial Registries (eg, www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (eg, basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions prior to the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data prior to the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the

costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.

- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
- Single Center Publication and Additional Publications: This is a multicenter study and is designed to be published with complete data from all the study sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter study and that the study was not intended, or statistically powered, for data presentation by a single study site.
- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this study to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and amendments, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

21. LIST OF REFERENCES

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APPENDIX A. SUMMARY OF CHANGES: PROTOCOL 747-401 VERSION 2 (DATED 22 MAY 2017)

Please note that Protocol 747 401 Version 1 was generated to specifically address US FDA post-marketing requirements but was not submitted to other Regulatory/Competent Authorities or Ethics Committees due to ongoing negotiations. The changes in Version 2 were incorporated based on FDA review of Version 1 of the protocol. In general:

- Background information was included to estimate the exposure difference between healthy subjects and patients with moderate hepatic impairment to support the rationale for dose selection (Section 5.4.2)
- Additional PK sampling times were added to adequately characterize the PK of OCA and its active metabolites at steady-state in patients with moderate and severe impairment when dosing weekly to biweekly (Section 12)
- The period between screening and Day 1 was extended to at least 14 days to establish a baseline for serum biomarkers with at least two samples two weeks apart (Schedule of Study Procedures, Section 9.7.4)
- The Week 3 contact Visit by email/telephone was changed to a Safety Visit to assess evidence of early hepatotoxicity (Schedule of Study Procedures, Section 9.7.6)
- Guidelines were added to assess patients for evidence of hepatotoxicity at each visit (Section 8.4.1.2).

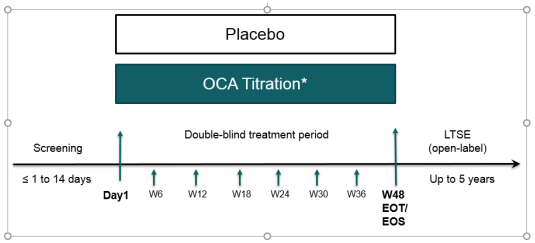
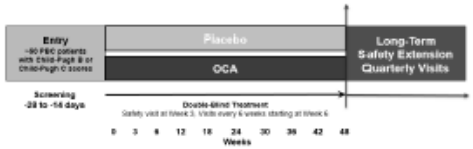
The table below includes substantial revisions made to Protocol 747-401 under Version 2. Revised text in Version 2 is indicated in bold font, and the text deleted from Version 1 is crossed out in the table below. (Minor/editorial changes and non-substantial changes are not listed individually in the summary table below).

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Title Page	~~**(For FDA Review Only)**~~	**EudraCT Number: 2017-001762-13**	Added EudraCT Number
STUDY PERSONNEL CONTACT INFORMATION	~~**Emergency Contact Information**~~ **Medical Monitor - ~~24-hour Emergency Reporting~~** Contact: PPD MD, Medical Director, ~~Drug Safety,~~ Intercept Pharmaceuticals, Inc. ~~Mobile:~~ PPD	**Medical Monitor** **Primary** Contact: PPD MD, Medical Director, **PI** Intercept Pharmaceuticals, Inc. (Intercept) Telephone: PPD Email: PPD	Updated contact list.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	Telephone: PPD Email: PPD ~~**Or if Not Available:**~~ ~~Contact:~~ PPD ~~MD, PhD, Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~**SAE Contact Information**~~ ~~SAE Fax:~~ PPD ~~SAE email address~~ PPD ~~Telephone~~ PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD ~~VP, Clinical Operations, Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~Mobile:~~ PPD ~~Fax:~~ PPD ~~Email:~~ PPD	SAE Fax: PPD SAE Email: PPD	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	The study is planned to have approximately ~~20~~ investigational sites, globally	The study is planned to have approximately **35** investigational sites, globally	Updated site numbers.
Synopsis, Study Period, 7.1.3, Study Duration	Studied Period: ~~The study~~ will ~~include a 14-day screening period and a 48~~-week double-~~blind primary~~ treatment period. ~~Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete~~ the ~~primary treatment~~ period ~~at which point all~~ patients will ~~transition~~ to ~~an open-label long-term safety extension (LTSE).~~	Study Period: **Patients** will **receive double-blind treatment for at least** 48 **weeks. Patients who have completed their 48**-week **double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week** treatment period and the **database for** that period **is locked (approximately 3 years)**. Patients will **then be given the option** to **go on** open-label **treatment**.	Updated description of study period.
Synopsis, Objectives 6.1 Primary Objectives; 6.2 Secondary Objectives, 6.3, Additional Objectives,	: ~~In patients with Moderate to Severe PBC:~~ • To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and OCA glucuronide – Liver biochemistry including total bilirubin – … aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT – – Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF 19), 7α hydroxy-4-cholesten-3-one (C4), and plasma ~~and fecal~~ bile acids • To assess the PK/Pharmacodynamic (PD) relationship of OCA on: □ ALP, total bilirubin, ~~and aminotransferases~~ □ Bile acid homeostasis □ Safety and tolerability ~~(eg pruritus)~~	• To evaluate the pharmacokinetics (PK) of OCA and its conjugates, glyco-OCA, tauro-OCA, and **metabolite** OCA glucuronide **compared with placebo** – Liver biochemistry including total **and direct** bilirubin – … aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT],), **international normalized ratio (INR), creatinine, albumin, platelets** – Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF 19), 7α hydroxy-4-cholesten-3-one (C4), and plasma bile acids • To assess the PK/Pharmacodynamic (PD) relationship of OCA with: □ **PK parameters compared to PD Parameters and Safety and Tolerability assessments (above)**	Clarified study objectives.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	• To assess clinical ~~outcomes~~ consistent with end-stage liver disease	• **To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ])** • To assess clinical **events** consistent with end-stage liver disease	
Synopsis, Methodology and Section 7.1. Overall Study Design	Patients will be screened ~~for up to ≤~~14 days…	Patients will be screened **≥14 days but not more than 28 days**…	Extended to 14 days to satisfy PMR for 2 baseline measurements.
Synopsis, Double-Blind Treatment Period, 7.1, Overall Study Design	Double-Blind ~~Primary~~ Treatment Period … (ie, Day 1 through Week 48), clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, ~~PK~~, and PD ~~(trough)~~. At each visit, ~~trough~~ PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12 ~~and only after a patient uptitrates~~. ~~Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the 48-week primary treatment period~~.	… Double-Blind Treatment Period: …(ie, Day 1 through Week 48), **an initial safety visit will occur at Week 3. After the Week 6, subsequent** clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. At each visit **(except screening and Week 3)**, **fasting** PK assessments will be performed in all patients participating in the study. Serial PK sampling will be performed at Week 12, **18, 24, 30, and 48.** **Patients who have completed their 48-week double-blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. Patients will then be given the option to go on open-label treatment.**	Updated description of study period.
Synopsis, Long-term Open Label Extension Phase	~~Long-term Open Label Extension Phase~~ ~~Once all patients have completed the double-blind 48-week primary treatment period, patients will have the option to continue into an open-label long-term safety extension and all patients will receive OCA. Visits in the LTSE will occur every 3 months for up to 5 years. Patients on placebo during the primary treatment period will initiate study medication at 5-mg OCA once weekly and follow the dosing regimen based on their CP score. Patients on OCA~~	Section deleted.	Updated description of study.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~during the primary treatment period will continue the dose that they are on once unblinded.~~		
Synopsis and Section 7.1.1, Study Design Diagram	 ~~EOS = end of study; EOT = end of treatment,~~ OCA = obeticholic acid *Initial dose titration of investigational product ~~may occur at the Week 12 Visit, or any study visit~~ …	 **Note:** Initial dose titration of investigational product may **be considered as early as the Week 12 visit**, or any study visit thereafter for patients on all dosing regimens, based on …. **Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.**	Updated study diagram.
Synopsis, Dosing Regimen, Section, 7.3 (Table 2)	All patients will initiate investigational product once weekly with 5 -mg OCA or matching placebo. ~~Starting~~ at Week 12, ~~safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below:~~ • ~~At Week 12~~, if investigational product is tolerated and laboratory assessments ~~from the Week 6 visit~~ do not indicate a safety concern, the patient ~~will change the dosing frequency~~ to 5 mg twice weekly, at least 3 days apart. • ~~Following an additional~~ 6 weeks ~~of treatment, if investigational product is tolerated,~~ patients ~~may be up-titrated to OCA~~ 10 mg twice weekly at least 3 days apart, the maximum dose for patients with CP-C. • Following an additional 6 weeks of treatment, if tolerated, Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, the maximum dose for patients with CP-B.	All patients will initiate investigational product once weekly with 5 mg OCA or matching placebo. **Titration may be considered as early as the Week 12 Visit. Following visit procedures** at Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient **may up-titrate to OCA 5** mg twice weekly **and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur** at least 3 days apart. **Every** 6 weeks **thereafter, based on safety and tolerability assessments**, patients **can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.** Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily. **Patients with CP-C may titrate to a maximum dose of OCA** 10 mg twice weekly at least 3 days apart.	Updated table for clarity.

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
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• ~~If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply.~~

Planned OCA or Matching Placebo Dosing Regimen by Child-Pugh Score
<table>
<tr><th></th><th colspan="2">Child-Pugh B (Moderate Hepatic Impairment)</th><th colspan="2">Child-Pugh C (Severe Hepatic Impairment)</th></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose [a] (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>5 mg once weekly</td><td>matching placebo</td></tr>
<tr><td>Titration 1[b] ~~(≥Week 12)~~</td><td>5 mg twice weekly[c]</td><td>matching placebo</td><td>5 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 2[b] ~~(≥6 weeks after Titration 1)~~</td><td>10 mg twice weekly[c]</td><td>matching placebo</td><td>10 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 3[b] ~~(≥6 weeks after Titration 2)~~</td><td>5 mg once daily</td><td>matching placebo</td><td>NA</td><td>~~matching placebo~~</td></tr>
</table>
~~[a]Starting dose based on patient's Child-Pugh Score at Screening.~~
[b]Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study.
[e]Dosing per the twice weekly schedule must be at least 3 days apart.
</td>
<td>
<table>
<tr><th></th><th colspan="2">Child-Pugh B (Moderate Hepatic Impairment)</th><th colspan="2">Child-Pugh C (Severe Hepatic Impairment)</th></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>5 mg once weekly</td><td>matching placebo</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo</td><td>5 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo</td><td>10 mg twice weekly[c]</td><td>matching placebo</td></tr>
<tr><td>Titration 3[a]</td><td>5 mg once daily</td><td>matching placebo</td><td>NA</td><td>NA</td></tr>
</table>
[a]Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability and/or changes in Child-Pugh Score at any time during the study
[b]Dosing per the twice weekly schedule must be at least 3 days apart.
</td>
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<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td></td><td>(insertion)</td><td>If, during the course of the study, a patient transitions from CP- B to CP-C, or vice versa, the maximal dose for the new CP classification would apply. If a patient demonstrates an improvement to CP-A, they should follow the dosing regimen for patients with CP-A.

Over the course of the study, a patient’s CP category may change. When a patient demonstrates a change in CP category, dosing should be reassessed and modified if appropriate. Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply. If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen should be followed.

Maximum Dose for OCA or Matching Placebo for Changes in Child-Pugh Category
<table><tr><th rowspan="2">Original Status</th><th colspan="3">New Status[a]</th></tr><tr><th>Child-Pugh A</th><th>Child-Pugh B</th><th>Child-Pugh C</th></tr><tr><td>Child-Pugh B</td><td>No change</td><td>No change</td><td>10 mg twice weekly[b]</td></tr><tr><td>Child-Pugh C</td><td>5 mg once daily</td><td>5 mg once daily</td><td>No change</td></tr></table>
[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for the planned dosing regimen.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.</td><td>Added to provide more information on dosing.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Synopsis and Section 8.2, Key Inclusion Criteria	2. Evidence of cirrhosis including at least one of the following: □ Biopsy ~~indicating cirrhosis or a medical history with histological evidence of cirrhosis~~ □ Clinical evidence consistent with cirrhosis including: ~~esophageal~~ varices, ascites, ~~encephalopathy,~~ or portal ~~hypertension~~ □ Liver stiffness as assessed by TE of ~~≥~~16.9kPa 6. ~~Age ≥18 years~~ 7. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate UDCA (no UDCA for ≥3 months) 8. ~~Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective method of contraception during the study and for 30 days after the end of treatment visit. Effective methods of contraception are considered to be those listed below:~~ ~~– Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm, with spermicide; or~~ ~~– Intrauterine device; or~~	2. Evidence of cirrhosis including at least one of the following: • Biopsy **results consistent with PBC Stage 4** • Liver stiffness as assessed by TE **Median Value** ≥16.9 kPa • Clinical evidence **in the absence of acute liver failure** consistent with cirrhosis including: **gastroesophageal** varices, ascites, **radiological evidence of cirrhosis (nodular liver or enlargement** of portal **vein and splenomegaly)** • **Combined low platelet count (<140 000/mm^3) with** – **persistent decrease in serum albumin, or** – **elevation in prothrombin time/INR (not due to antithrombotic agent use), or** – **elevated bilirubin (2× ULN)** 6. Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 1, or unable to tolerate **or unresponsive to** UDCA (no UDCA for ≥3 months)	Provided more details regarding inclusion requirements. Only listed inclusions directly related to PBC in synopsis. Other criteria were deleted from synopsis but remain in the main body. Only criteria with changes are presented in this SOC. The full inclusion/ exclusion list is in the body of the protocol.

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	– ~~Vasectomy (partner), or~~ – ~~Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection, or~~ – ~~Abstinence, if in line with the preferred and usual lifestyle of the patient (where abstinence is defined as refraining from heterosexual intercourse)~~ 9. ~~Must provide written informed consent and agree to comply with the study protocol.~~		
Synopsis and Section 8.3, Key Exclusion Criteria	4. History or presence …: – Hepatitis C virus infection RNA positive 5. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function~~ during the Screening period~~ 6. ~~Patients with history or presence of hepatorenal or hepatopulmonary syndrome~~ 7. ~~Patients with significant active infection (ie spontaneous bacterial peritonitis)~~ 8. ~~Patients with known or suspected hepatocellular carcinoma~~ 9. ~~History of known or suspected clinically significant hypersensitivity to OCA or any of its components~~ 10. ~~Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening. Participation in a previous study of OCA is allowed with 3 months washout prior to enrollment in this study~~	4. **Hepatic encephalopathy (as defined by a West Haven score of ≥2)** 5. History or presence …: – Hepatitis C virus infection **and** RNA positive 6. In the opinion of the Investigator, fluctuating or rapidly deteriorating hepatic function~~ ~~**prior to randomization**	Added additional **key** exclusion criteria #4. Other criteria were deleted from synopsis but remain in the main body. Only criteria with changes are presented in this SOC.

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	11. ~~Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain~~ 12. ~~UDCA naïve (unless contraindicated).~~				
Synopsis, Duration of Treatment	~~The study will include a 14-day screening period and a 48 week double-blind primary treatment period. Following completion of the Week 48 visit, patients will remain on blinded investigational product and be seen at regular visits every 3 months until all patients complete the double-blind 48-week primary treatment period. Hence, depending on the rate of patient enrollment, patients will be exposed to investigational product for a minimum of 1 year up to approximately 2 years during the blinded period. Following completion of the blinded period, Patients will have the option to continue into an extension during which they will receive open-label treatment and be seen at regular visits every 3 months for up to 5 years.~~		**Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment.**		Updated description of study.
Synopsis, Criteria for Evaluation and 11, Overview of Assessments, Table 5, Additional Objectives	~~PD Parameters;~~	plasma, ~~fecal~~ bile acids	**PK**	**Plasma concentrations of OCA and its conjugates, glyco-OCA, tauro-OCA; and metabolite OCA glucuronide**	Clarified study parameter for evaluation.
	Changes in MELD and in CP score		Changes in MELD and in CP score **and components of the CP score**		

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	PD parameters	~~fecal~~ bile acids	**PK**/PD parameters	bile acids	
	Markers of inflammation	IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30, ~~and others as determined during course of study.~~		IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30,	
	~~PK/PD relationship of OCA and liver biochemistry~~	~~OCA and its conjugates, glyco-OCA tauro-OCA; and OCA glucuronide~~	PK/PD relationship	**PK parameters compared to PD Parameters and Safety and Tolerability assessments (above**)	
	~~PK/PD relationship of OCA and bile acid homeostasis~~	~~Bile acids~~			

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	Clinical ~~Outcomes~~	Incidence and time to first occurrence of any of the following: all-cause mortality, liver-related events resulting in death, hepatic failure leading to liver transplant, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, ~~hepatocellular carcinoma~~	Clinical **Events**	Death (all-cause and liver-related), liver transplant, Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline), Hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, Uncontrolled ascites, and HCC.	
Synopsis, Statistical Methods, Safety Analyses	The absolute change from baseline will also be summarized. No inferential comparison ~~of safety endpoints~~ will be performed.		The absolute change from baseline will also be summarized. No inferential comparison **with formal statistical hypothesis testing** will be performed **for safety endpoints.**		Clarified statistical methods.
Synopsis, Statistical Methods, Additional Efficacy Analyses	The following clinical ~~outcomes~~ will be captured in the study: • ~~All~~-cause ~~mortality~~ • Liver related death • Liver transplant		The following **endpoints consistent with end-stage liver disease** will be captured in the study: • **Time to death** (all cause) • **Time to** liver-related death • **Time to** liver transplant		Clarified statistical methods.

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	• Variceal bleed • Hepatic encephalopathy • Bacterial peritonitis • ~~Ascites~~ • ~~Hepatocellular carcinoma~~ The incidence and time to first occurrence of any of the above listed clinical outcomes will be summarized ….The tabulation will include the KM ~~estimate of the medians~~ and corresponding 95% confidence intervals (CIs), ~~if the medians can be estimated~~. … The hazard ratio and 95% CI will be estimated based on a Cox regression model stratified by randomization strata. In addition, the incidence and time to each of the above ~~outcomes~~ will be summarized by treatment group using the same methods as defined above.	• **Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)** • **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:** – **Time to** variceal bleed – **Time to** hepatic encephalopathy **(as defined by a West Haven score of ≥2)** – **Time to spontaneous** bacterial peritonitis **(confirmed by diagnostic paracentesis)** • **Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)** The incidence and time to first occurrence of the above listed clinical outcomes will be summarized ….The tabulation will include the KM **methodology using 25th, 50th (median),** and **75th percentiles with associated 2-sided** 95% confidence intervals (CIs), **as well as percentage of censored observations**. …. The hazard ratio and **2-sided** 95% CI will be estimated based on a Cox regression model stratified by randomization strata. In addition, the incidence and time to each of the above **clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC)** will be summarized by treatment group using the same methods as defined above.	

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Synopsis and Section 15.2, Sample Size,	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients per OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. ~~The assessment was based on 80% powering for the 90% confidence interval of the geometric mean ratio of Total OCA (sum of OCA, glyco-OCA, and tauro-OCA).~~	To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. Ten patients on placebo will be included as a comparator. **An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.**	
5.2, Nonclinical Experience with Obeticholic Acid	Insertion	**Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the detergent effects of a bile acid at exceedingly high hepatocellular exposure.**	Added section to briefly address nonclinical studies.
5.3, Clinical Development of Obeticholic Acid	As of 31 Jan 201~~6~~, approximately ~~1726~~ patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ patients had PBC, ~~330~~ patients had nonalcoholic steatohepatitis, 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease, 33 patients had alcoholic cirrhosis/portal hypertension, ~~and~~ ~~20~~ patients had primary sclerosing cholangitis (PSC).	As of 31 Jan 201**7**, approximately **2186** patients have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** patients had PBC, **686** patients had nonalcoholic steatohepatitis (**NASH**), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (**NAFLD**), 33 patients had alcoholic cirrhosis/portal hypertension**,** **52** patients had primary sclerosing cholangitis (PSC), **and 5 patients had biliary atresia.**	Updated numbers of patients who have received OCA.
5.4, Rationale for Study Design and Dose for Investigational Product		**5.4 Rationale for Study Design and Dose for Investigational Product**	Inserted new header for clarity
5.4.1, Rationale for Study Design	~~Patients with moderate or severe hepatic impairment (Child Pugh B or C) will constitute approximately 20% of the patients included in the ongoing clinical outcomes Study 747-302 which was~~ specifically designed to confirm clinical benefit across the spectrum of disease including patients	**The 747-401 study is** specifically designed to confirm clinical benefit across the spectrum of disease including patients with hepatic impairment**.** Data collected from Study 747 401 will serve as a bridge to the **747-302 study.**	Clarified the intent of the 401 study.

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	with hepatic impairment. Data collected from Study 747 401 will serve as a bridge ~~between~~ the ~~two studies.~~		
5.4.2, Rationale for Obeticholic Acid Dose and Duration	~~Results from the hepatic impairment study (747-103) indicate that plasma exposure increases, in comparison to subjects with normal liver function, with increasing severity of impairment as classified by Child Pugh A (CP-A), CP-B or Child Pugh C (CP-C) scores by 1.4 , 8.0 , and 13-fold, respectively. No apparent impact on the overall safety profiles were observed in this study. Liver exposure, however, modestly increased by 1.1 , 1.5, and 1.7-fold, respectively, as shown in simulations using a physiologic PK model developed to characterize OCA and its conjugates.~~ Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure. (insertion)	**Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (CP Score). Model simulations predicted that for mild (Child-Pugh A [CP-A]), moderate (Child-Pugh B [CP-B]), and severe (Child-Pugh C [CP-C]) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to patients with normal hepatic function, whereas total OCA liver concentrations increase 1.1-, 1.5-, and 1.7-fold, respectively. Because the liver is the primary site of action for the safety and efficacy of OCA, it is important to account for the differences in systemic and liver exposure when assessing effective doses. It is also important to note that while hepatically impaired (CP-B and C) patients treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy patients, no apparent impact on the overall safety profile was observed, consistent with only a modest increase in liver exposure of OCA associated with hepatic impairment. Together, the results from these analyses suggest that the doses of OCA administered to patients with moderate or severe hepatic impairment should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.** **Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower**	Added rationale for OCA dosing in hepatically impaired patients.

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	Therefore, a modified dosing regimen is recommended for OCA in patients with moderate and severe hepatic impairment that is designed to initiate doses to achieve plasma exposures levels of OCA similar to those without hepatic impairment or CP-A. After which, subjects may then titrate their doses upwards to achieve liver exposures that would be similar in both patient populations. ~~This modified dosing regimen was selected based on the established safety and tolerability of OCA in subjects with PBC, along with PK/PD modeling and simulations.~~ ~~Patients will initiate dosing at OCA 5 mg once weekly. Starting at Week 12, if the prior dose regimen was tolerated, the patients will increase the dosing frequency to 5 mg twice weekly (at least 3 days apart). After 6 weeks, a second titration may occur to OCA 10 mg twice weekly as long as tolerated. Patients classified as CP-B may further titrate their dose upwards to OCA 5 mg once daily after 6 weeks on the OCA 10 mg twice weekly regimen.~~	**dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).** **The dosing regimen in this study follows the FDA-approved prescribing information, with the exception of the maximum allowed dose in patients with moderate impairment. While the prescribing information allows for a maximum dose of 10 mg twice weekly for patients with moderate impairment, the protocol allows for a maximum dose of 5 mg once daily. The choice of 5 mg once daily is supported by the estimated steady-state liver and plasma exposure of total OCA for patients with moderate hepatic impairment receiving a 5 mg once daily dose relative to healthy patients receiving a 10 mg dose. A maximum allowed dose of 5 mg once daily in patients with moderate hepatic impairment is estimated to achieve liver exposure similar to non-hepatically impaired patients receiving a 10 mg daily dose and maximize efficacy in this patient population.**	
7.1.2, Schedule of Study Procedures	Schedule of Study Procedures ~~(Double-Blind Treatment Period)~~	Schedule of Study Procedures	Updated procedures to match updated study design.
7.1.2, Schedule of Study Procedures, Visit Windows	~~≤ 1~~ to -14 days	**-28** to -14 days	Updated procedures to match updated study design.
7.1.2, Schedule of Study Procedures, Visit Weeks Row	Week 3: ~~Safety Contact~~ Week 48 Under Long-Term Treatment	Week 3 Week 48/**ET/EOS/EOT** **Every 3 months**	Week 3 telephone/email contact visit now a

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			laboratory safety visit.
7.1.2, Schedule of Study Procedures	(Insertion) Dose Titration IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30, ~~others as determined during course of study~~ ~~Fecal PK Analysis~~ ~~TE Fibroscan®~~ ELF ~~MELD~~ PK ~~trough~~ Collection	Column: **Long-Term Treatment** Procedures: **Medical and Surgical Procedures** Dose Titration **Assessment** **Markers of Inflammation:** IL-6, hs CRP, TNF-α, IgM, IgG, IgA, CK-18-M30 • **TE**/ELF **(HA, P3NP, and TIMP 1)** PK **Fasting** Collection	Updated procedures to match updated study design
7.1.2, Table 1, Schedule of Study Procedures Footnotes	~~a~~ Patients should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week 3 and continuing to Week 48 to assess for AEs, concomitant medications, and verify that s/he is dosing as directed. b ~~Visits should be based on Day 1.~~ ~~c~~ The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits ~~(except Screening Visit 1)~~ but water is permitted. ~~d Medical history performed at Screening only.~~ ~~e The yearly physical exam will also include an~~ assessment of smoking and alcohol consumption history and current habits ~~for both~~. ~~Height~~ will ~~only~~ be collected at Day 1 and Week 48. ~~f~~ Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF. ~~g~~ The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated	**aVisit schedule should be based on Day 1. Day 1 visit must occur at least 2 weeks after screening visit.** [b]**Patients** should be contacted by telephone/email every 3 weeks (±1 week) between clinic visits starting at Week **9** and continuing to Week 48 to assess for AEs, concomitant medications, **medical/surgical procedures**, and verify that s/he is dosing as directed. [c] **Preferably, the patient comes in to the clinic for this visit. Alternatively, site will telephone the patient for assessments and home health nurse will visit to draw safety labs.** [d] **Visit should occur 3, 4, or 5 days after taking the Week 6 dose.** **e** The patient should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, **including screening**, but water is permitted. f **Height and** assessment of smoking and alcohol consumption history and current habits will be **assessed** at **Screening** and Week 48. **Assessment of smoking and**	Updated procedures to match updated study design

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	translation is not available in the local language required for a specific study patient, the ~~data from that~~ questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease. ~~h~~ Patients will be instructed to begin dosing on the Day 1 visit after completing all study assessments. ~~(ie, on Day 1~~). Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet. ~~i~~ ~~Initial~~ dose titration of investigational product may occur at the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score. j Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally)	**alcohol consumption history and current habits will be assessed quarterly after Week 48.** g Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central laboratory evaluations per the Child-Pugh scoring system noted in the eCRF. h The EQ-5D-5L Quality of Life questionnaire is validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study patient, the questionnaire will not be collected. The CLDQ measures change over time in patients with chronic liver disease. **i New investigational product bottles will be dispensed if the patient is titrated. Unless up-titrated, patients are expected to use up each investigational product bottle before a new bottle will be dispensed. No new bottles will be dispensed if dose frequency is changed**. Patients will be instructed to begin dosing **on Day 1**, after completing all study assessments. Patients will be instructed to take investigational product at approximately the same time of day. Patients must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet. **j** Dose titration of investigational product may occur starting **after the** Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on CP score, tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability and CP score. **k** Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit **(except Week 3**). If positive, a confirmatory blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the patient may not continue in the study. (Additional testing may be conducted where required, regionally).	

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		l The patient will be given the option to return to the clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling. **m The noninvasive radiological liver fibrosis measurement devices (such as, FibroScan® device [Echosens; Paris, France]) will be used at all study sites to collect hepatic stiffness measurements.** **n Patients will complete a TE/ELF and ultrasound assessment, every 6 months (±2 weeks) after Week 48.** **o ECG and urine dipstick will be done yearly (±2 weeks) after Week 48 Visit.** **p Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm suspected HCC.**	
7.1.3, Study Duration	~~The study will include a 14-day screening period and a 48-week double-blind primary treatment period. Following completion of the primary treatment period, patients will remain on blinded investigational product and be seen at regular intervals until all patients complete the primary treatment period (Figure 1). Patients will have the option to continue into an open-label LTSE after all patients have completed the Week 48 procedures in which they will receive open-label treatment and be seen at regular visits every 3 months for up to 5 years.~~	**Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked (approximately 3 years). Patients will then be given the option to go on open-label treatment**.	Updated description of study period.

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7.3, Planned Dosing Regimen	All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. ~~Starting~~ at Week 12, ~~safety and tolerability of investigational product will be evaluated and, if tolerated, the patient can increase the dose to the next dose level as described below (Table 2):~~ • ~~At Week 12,~~ if investigational product is tolerated and laboratory assessments ~~from the Week 6 visit~~ do not indicate a safety concern, the patient will ~~change the dosing frequency to~~ 5 mg twice weekly, at least 3 days apart. ~~Following an additional 6 weeks of treatment, if investigational product is tolerated, patients may be up titrated to OCA~~ 10 mg twice weekly at least 3 days apart, ~~the maximum dose for patients with CP-C~~ ~~Following an additional~~ 6 weeks ~~of treatment, if tolerated~~, patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily, ~~the maximum dose for patients with CP-B~~.	All patients will initiate investigational product once weekly with 5-mg OCA or matching placebo. **Titration may be considered as early as the Week 12 visit. Following visit procedures at** Week 12, if the investigational product is tolerated and laboratory assessments do not indicate a safety concern, the patient will **up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur** at least 3 days apart**. Every 6 weeks thereafter, based on safety and tolerability assessments, patients can be considered for further up titration as described below (Table 3). At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.** **Patients with CP-C** may titrate **to a maximum dose of** OCA 10 mg twice weekly at least 3 days apart. Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.	Clarified dosing regimen.
7.4, Dose Adjustment Criteria, Scheduled Dose Titration	~~The first dose titration for any patient may occur no earlier than 12 weeks following~~ initiation of OCA or matching placebo.	**After** initiation of OCA or matching placebo, **titration may be considered as early as the Week 12 visit.**	Clarified dosing regimen.
7.4.1, Pre-Titration Tolerability Assessment Requirements	Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. ~~A review of AEs and available safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within approximately 6 weeks of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigational product (eg, Week 6, laboratory results should be reviewed prior to titration at Week 12). If for any reason, laboratory results are not available at the time of the~~	Tolerability of investigational product must be assessed prior to titrating a patient to a higher dose. **To determine if a patient is eligible for a dose up-titration refer to Section 7.3**	Clarified dosing regimen.

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	~~planned up titration visit, additional laboratory samples must be obtained and reviewed, prior to up titrating the patient to a higher dose. 7.3~~ ~~To be eligible for a dose up titration, patients should not be experiencing significant AEs that are suspected to be related to investigational product (eg, severe pruritus) or displaying other symptoms that may indicate intolerability of investigational product.~~		
7.4.2., Safety Criteria for Adjustment or Stopping Doses	~~Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.~~ ~~Subjects who discontinue investigational product are expected to continue in the study (and follow the regular visit schedule) until the end of the study, and the study will only terminate at the time.~~		This information has been incorporated into Section 8.4, which was renamed 8.4. Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study and additional text was added.
8.4, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	8.4 ~~Patient~~ Withdrawal ~~Criteria~~ (Insertion)	**Dose Adjustment, Interruption, and** Withdrawal **from Investigational Product or Study** **Investigational product may be temporarily decreased (eg, by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be resumed to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.**	Section revised to integrate withdrawal criteria in one section of protocol. Text was

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		Patients who are discontinued from investigational product prior to completion of the study are encouraged to continue to follow the regular visit schedule, with the exception of PK sampling, but may withdraw consent at any time.	previously in Section 7.4.2.
8.4.1. Reasons for Additional Monitoring or Mandatory Interruption of Investigational Product	8.4.~~1~~. Reasons for Mandatory Discontinuation of Investigational Product	Moved to 8.4.**2** 8.4.1. Reasons **for Additional Monitoring** or Mandatory Interruption of Investigational Product	Heading text updated.
8.4.1.1, Reasons for Additional Monitoring Related to Liver Chemistries	8.4.1.1. ~~Pregnancy~~	8.4.1.1. **Reasons for Additional Monitoring Related to Liver Chemistries** **Patients who develop ALT or AST >2x baseline (and >ULN) or total bilirubin >1.5x baseline (and >ULN) should have repeat testing within 48 to 72 hours to confirm values. Patients with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or INR with persistent increases in ALT or AST should also be closely monitored.**	Pregnancy moved to Section 8.4.1.3. New Section with text added.
8.4.1.2. Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	(Insertion)	8.4.1.2. **Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries** **Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3× baseline (and >ULN)** • **Total bilirubin >2× baseline (and >ULN)** **Repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing should be performed. Detailed adverse event information should also be collected, and the patient should be investigated for possible causes of the liver chemistry changes, as appropriate. The Investigator**	New Section added to meet PMR requirements.

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		should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable. **If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), patients should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms.** **For the purposes of this protocol, if the above referenced significant elevation in liver enzyme or bilirubin levels resolve following interruption of investigational product and no other cause for the elevation is identified, the elevations should be assumed to be related to investigational product and investigational product should be discontinued. If the liver enzyme or bilirubin levels do not resolve following interruption of investigational product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the patient may be re-challenged following a discussion between the Investigator or designee and the Sponsor.** **Elevation of liver enzymes or bilirubin is based on comparison to baseline values defined as the mean of all available Screening and Day 0 values, which are the mean of all available evaluations prior to the first administration of investigational product. At least 2 of these samples will be obtained a minimum of 2 weeks apart during the Screening period. Elevations that occur gradually over the course of the study may be indicative of disease progression and should be assessed as clinically appropriate. Liver enzyme and bilirubin elevations that occur over a shorter time, such as within a 6-month period, should be evaluated for drug-induced liver injury as provided in the guidelines below.**	

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		If at any time a patient develops signs or symptoms of hepatotoxicity such as new onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>7%) in combination with elevations in liver enzymes, investigational product should be interrupted and liver enzymes monitored until signs or symptoms resolve. **Patients who develop evidence of severe drug-induced liver injury that is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged. Severe drug-induced liver injury includes, but is not limited to, functional hepatic impairment, as indicated by rising bilirubin or INR that cannot be explained by progression of disease. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.** **If after all investigations and actions outlined above have been completed, the investigator determines that the elevations in liver biochemistries are considered not related to investigational product, the Sponsor must be contacted before investigational product can be reinitiated. Follow-up procedures for patients resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment. Results must be reported to the site as soon as possible so the Investigator can determine if it appropriate for the patient is to continue treatment.** **The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.** **All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 15.9)**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
8.4.1.3, Pregnancy	(Insertion) ~~Whenever the site is notified of a possible pregnancy, the patient should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female patient becomes pregnant, the patient must stop taking investigational product immediately and be withdrawn from the study~~…	8.4.1.3. **Pregnancy** **If a female patient becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 13.1.10 pregnancy is not considered an AE for reporting purposes. The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 13.1.10). New baseline procedures should include pregnancy testing**.	Was Section 8.4.1.1
8.4.2, Reasons for Mandatory Discontinuation of Investigational Product	8.4.2. ~~Other Reasons for Discontinuation of Investigational Product or Study Termination~~	8.4.2. Reasons for Mandatory Discontinuation of Investigational Product **Patients who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these patients should be encouraged to consent to the semiannual telephone contact and/or continued record review only to allow for secondary outcome events data to be collected.**	Now Section 8.4.3 and text added.
	~~8.4.2.3. Elevated Liver Enzymes~~	Section deleted.	Information in 8.4.1.2 now covers this.
8.4.3, Other Reasons for Discontinuation of Investigational Product or Study Termination	~~Subjects who discontinue investigational product are expected to continue in the study until the end of the study or at the discretion of the Sponsor. If a patient experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe.~~ ~~Early termination procedures should only be conducted if the patient withdraws consent (See Section 9.7.14).~~	8.4.3. **Other Reasons for Discontinuation of Investigational Product or Study Termination** The following events are considered appropriate reasons for **a patient to discontinue investigational product; however, these patients are expected to continue in the study until study termination (or at the discretion of the Sponsor):** • **Patient begins treatment with commercially available OCA.** • **The Investigator or Sponsor considers that it is advisable or in the best interest of the patient.**	Was Section 8.4.2 and additional text added.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~It is agreed that, for reasonable cause, either the Investigator or the Sponsor, may terminate this study.~~ ~~The following events are considered appropriate reasons for a subject to discontinue from the study:~~	• **The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to study drug.** • **Withdrawal of consent** – **Consent may be fully withdrawn (in which case the patient discontinues both investigational product and study visits and procedures).** – **Consent may be modified to discontinue study visits but allow semi-annual telephone contact.** – **Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE) and liver-related clinical outcomes.** – **Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.12)**	
8.4.3.1. Withdrawal of Consent to Continue in the Study	8.4.3.1. Withdrawal of Consent … their consent to continue in the study at any time (Insertion) A reasonable effort must be made to…	**8.4.3.1. Withdrawal of Consent to Continue in the Study** **Early termination procedures should be conducted if the patient withdraws consent (See Section 9.7.12).**	Added more information regarding withdrawal from study.
8.4.3.2. Lost to Follow-Up	8.4.2.2. Lost to Follow-Up ~~If a patient fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the patient, he or she~~ will be ~~withdrawn from the study~~.	**8.4.3.2. Lost to Follow-Up** **Patients** will be **considered "lost to follow up" only after documented attempts to reach the patient prove unsuccessful.**	Updated text.
8.4.4, Patient Discontinuation Notification	8.4.~~3~~. Patient Discontinuation Notification The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the	8.4.**4**. Patient Discontinuation Notification The Investigator must notify the Sponsor as soon as possible if any patient prematurely discontinues from the study. The date when the patient is withdrawn and the primary reason(s)	Clarified text.

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	primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. ~~Patients will be considered "lost to follow up" only after reasonable, documented attempts to reach the patient prove unsuccessful. In all cases, a reasonable effort must be made to determine the reason(s) that a patient fails to return for required study visits or discontinues from the study.~~ This information must be documented in the eCRF.	for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. This information must be documented in the eCRF.	
9.2, Concomitant Medications	~~Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section) during the study.~~ Concomitant medications will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). … taken ~~prior to (ie~~, within 30 days of Screening~~)~~ and … Concomitant medications should be stable prior to Day 1 ~~(ie no change in dosing within 3 months of screening).~~	Concomitant medications (**other than prohibited concomitant medications listed in Section 9.2.2**) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). … taken within 30 days of Screening and during the study must be recorded in the source documents and … Concomitant medications should be stable prior to Day 1.	Clarified use of concomitant meds**.**
9.2.1, Drug Interactions	~~Patients taking~~ bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be ~~instructed to stagger their dosing~~ of investigational product and UDCA, ~~ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (and UDCA;~~ ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration).	Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should **not** be **taken within 4 hours** of **taking investigational product (**and UDCA **if applicable),** ie, BAS should be administered at minimum 4 hours before or 4 hours after investigational product administration)**.**	Clarified use of concomitant meds.
9.2.2, Prohibited Medications	Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.~~2~~). ~~Fibric acid derivatives (fibrates) and other medication intended to lower blood triglyceride levels are also prohibited while on investigational product.)~~	Patients who continue with commercial OCA therapy must discontinue investigational product and are expected to continue through the end of the study (see Section 8.4.**3**).	Some patient may be expected to be on fibrates.
9.4.2, Blinding	The patients, Investigator, and study site staff will be blinded to…	The **Sponsor**, patients, Investigator, and study site staff will be blinded to…	

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9.6, Restrictions	Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited.	Participation in another investigational product, biologic, or medical device study within 30 days prior to Screening and during the course of the study is prohibited. **Previous exposure to OCA (as a study participant or received commercial OCA therapy) is allowed within 3 months prior to enrollment in this study**	Updated to include patients who may be on prescribed OCA and who received investigational OCA as study participants.
9.7.1, Visit Procedures	(Insertion)	**Visit windows are specified in the Schedule of Study Procedures (Table 1).**	Added text pointing to visit windows for study procedures.
9.7.2, Informed Consent Procedures	…The patient must be willing and able to provide written informed consent (on hard copies ~~or on electronic devices such as iPads)~~ before entering the study.	The patient must be willing and able to provide written informed consent (on hard copies) before entering the study.	Updated language.
9.7.3, Assessing Cirrhosis	~~To determine which dosing regimen patients should follow, cirrhosis should be assessed by the Investigator at Screening Visit 1.~~ Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators: – varices ~~Patients will be dosed according to their CP Score calculated in the eCRF (see Section 14.1.1 and Table 12).~~ ~~Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in cirrhosis status will necessitate re-evaluation of the dosing regimen.~~	Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of the study are defined as a patient who has documented evidence or presence of one or more of the following cirrhosis indicators: – **Gastroesophageal** varices	Clarified assessment instructions.

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9.7.4, Screening Procedures	Screening Procedures ~~(1 day to~~ 14 days prior to Day 1)	Screening Procedures (14 days **to 28 days** prior to Day 1)	Updated procedures to match updated protocol design.
	The Screening Visit assessments must be performed ~~within~~ ≤14 days prior to Day 1 to…	The Screening Visit assessments must be performed ≥14 days prior to Day 1 to…	
	The patient is to review and sign the ICF	• **Verify that the patient has fasted for at least 8 hours.** – **Record fasting status in the source and eCRF** – **If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits**	
	~~• Obtain blood samples for serum chemistry, hematology, and coagulation tests.~~		
	• Perform a physical examination.	Perform a physical examination, **including smoking and alcohol consumption history, and current habits for both.**	
	(Insertion)	• **Record the visit in IWRS**	
	• Perform TE using the Fibroscan® TE device. ~~If TE has been done within 3 months of Day 1 and a report/adequate data are available, a pretreatment TE at Day 1 is not required.~~ If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	• Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~• Provide kits and instructions for collection of stool specimens at home prior to the Day 1 visit~~	• Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required. If the ultrasound cannot be performed at Screening (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed anytime within the screening visit window or on Day 0. Results from the screening ultrasound should be reviewed to assess possible exclusion criteria prior to randomization.	Clarified sampling procedures.
9.7.5, Day 1 Procedures	☐ ~~Obtain blood samples for~~ markers of inflammation ☐ ~~ELF (including~~ HA, P3NP, and TIMP-1) ☐ ~~Trough~~ PK assessment	Markers of inflammation and fibrosis (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK -8-M30, HA, P3NP, and TIMP 1) **Fasting** PK assessment	Clarified sampling procedures
	…, after patient eligibility has been confirmed	… after patient eligibility has been confirmed. **Instruct the patient to take Day 1 dose on the day of this visit.**	Clarified procedures
	• Record the visit in IWRS and dispense investigational product ☐ Instruct the patient to begin dosing on the day. (Second to last bullet) …the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed.	• Record the visit in IWRS and dispense investigational product – Instruct the patient to begin dosing on the day **of the Day 1 visit.** …the procedure may be completed within the Day 1 visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 visit, preferably, after patient eligibility has been confirmed. **Instruct the patient to take Day 1 dose on the day of this visit.**	Updated procedures to match updated protocol design.

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9.7.6, Week 3 Safety Visit Procedures	Week 3 ~~(~~Safety ~~Contact)~~	Week 3 Safety **Visit Procedures**	Updated procedures to match updated protocol design per PMR requirements.
	~~Patients should be contacted by telephone at Week 3 to assess for AEs and verify that s/he~~ is dosing as directed. • ~~Contact~~ patient ~~by phone/email~~.	**Preferably, the patient will come in to the clinic for this visit. Alternatively, the site will telephone the patient for assessments and a home health nurse will visit to draw safety labs.** **Verify that patient** is dosing as directed. • **Verify that the** patient **has fasted for at least 8 hours.** □ **Record fasting status in the source and eCRF** • **If the patient reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the patient that fasting is required prior to all study visits.** • **Review and record prior concomitant medications.** • **Assess and record AEs.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess investigational product compliance, perform investigational product accountability**	
		• **Obtain blood samples for** □ **Serum chemistry, hematology, and coagulation** **Schedule the next visit, reiterate dosing instructions, and advise the patient:** **Week 6 visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 visit within the following Wednesday and Friday (Figure 2).** • □ **NOT to take investigational product on the morning of the next visit, and**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		☐ **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** ☐ **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.**	
9.7.8, Week 9 through Week 48 (Safety Contact)	(Insertion)	**Patients should be contacted by telephone/email at Week 9 and every 3 weeks afterward to Week 48.** • **Contact patient by phone/email.** • **Review and record prior concomitant medications.** • **Assess and record AEs.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess investigational product compliance, perform investigational product accountability.**	Section added to provide guidance for telephone/email safety contact.
9.7.9, Week 12, Week 24, Week 36 Procedures	Week 12 Procedures Obtain blood samples ~~for markers of inflammation~~ ☐ ~~ELF (including HA, P3NP, and TIMP-1)~~ ☐ C4, ~~and~~ FGF-19, ~~bile acids~~ ☐ ~~Trough~~ PK assessment	Week 12, **Week 24, Week 36** Procedures • **Assess investigational product compliance, perform investigational product accountability** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible. (Refer to Section 7.3)** • Obtain blood samples for ☐ **Serum chemistry, hematology, and coagulation** ☐ **Markers of Inflammation (IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30)** ☐ **Bile Acid**/C4/FGF-19	Updated procedures to match updated protocol design.

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		□ **Fasting** PK assessment • **Perform a urine-based β-hCG pregnancy test in females of childbearing potential.** • **Perform TE using the Fibroscan® TE device. If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit.**	
	• Serial PK assessment; the following procedures will be conducted in all patients	• Serial PK assessment at **Week 12 and 24 ONLY (not done at Week 36 and Week 42);** the following procedures will be conducted in all patients	Updated procedures to match updated protocol design.
9.7.9, Week 12, Week 24, Week 36 Procedures	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
	Insertion	• Perform an ultrasound for HCC surveillance at **Week 24 ONLY** (if equipment is unavailable, sites should make every attempt to use available community referral sites).	
	• ~~Assess the patient's supply of investigational product to ensure an adequate amount.~~	deleted	Deleted for clarity.
9.7.10 Week 18 and Week 30 Procedures		Added the following procedure: • **Dispense investigational product only if there is dose increase or as needed. No new IP bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each IP bottle before a new bottle will be dispensed.**	Section merged into 9.7.8, additional PK assessments added per

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~□~~ Obtain blood samples ~~for markers of inflammation~~ □ ~~ELF (including HA, P3NP, and TIMP-1)~~ □ C4, ~~and~~ FGF-19, ~~bile acids~~ □ ~~Trough~~ PK assessment Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 hours post dose	• Obtain blood samples for – **Serum chemistry, hematology, and coagulation** – **Markers of inflammation and fibrosis (IL 6, hs-CRP, TNF α, IgM, IgG, IgA, CK 18 M30, ELF [HA, P3NP, and TIMP 1])** – **Fasting** PK assessment – **Bile Acid**/C4/FGF-19 • Serial PK assessment at **Week 12 and 24 ONLY (not done at Week 36)**; the following procedures will be conducted in all patients:□ Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6 **7, 8, 9, and 24** hours post dose	PMR requirements.
	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume a **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
9.7.10, Week 24 Procedures	~~9.7.10, Week 24 Procedures~~	deleted	Incorporated into Section 9.7.8
9.7.11, Week 48 Procedures	9.7.1~~2~~	9.7.10**, Week 48 Procedures**	Updated language.
	• Perform a physical examination,	• Perform a physical examination, **including smoking and alcohol consumption history, and current habits for both**	Clarify study procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	(Insertion)	• **Assess investigational product compliance, perform investigational product accountability.** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible (refer to Section 7.3)** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	Clarify study procedures.
	Obtain blood samples ~~for markers of inflammation~~ □ ~~ELF (including HA, P3NP, and TIMP-1)~~ □ C4, ~~and~~ FGF-19, ~~bile acids~~ □ ~~Trough~~ PK assessment	• **Perform urinalysis (dipstick)** • Obtain blood samples for – **Serum chemistry, hematology, and coagulation** – **Markers of inflammation and fibrosis (IL 6, hs-CRP, TNF α, IgM, IgG, IgA, CK 18 M30, ELF [HA, P3NP, and TIMP 1])** – **Fasting** PK assessment – **Bile Acid**/C4/FGF-19	Clarify study procedures.
	• Serial PK assessment; will ~~only~~ be conducted in patients ~~who are uptitrating to the next dose level.~~	• Serial PK assessment; **the following procedures** will be conducted in **all** patients.	Updated language.
		Immediately following 1 hr post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes)	Added more sampling times.

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		□ Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, **7, 8, 9, and 24** hours post dose.	
	Note: Patients should ~~not~~ consume any food for the duration of the ~~6-hour PK assessments except the meal replacement drink.~~	Note: Patients should only consume **meal following the 4-hour and 7- hour PK assessment times (see Figure 3).**	Added more sampling times.
	Perform TE using the Fibroscan® TE device.	Perform TE using the Fibroscan® TE device. **If the TE cannot be performed on visit day (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.),** the **procedure may be completed within the visit window (if data is needed for cirrhosis assessment) or as close as possible to the visit**.	Clarified procedural instructions.
	• ~~Assess the patient's supply of investigational product to ensure an adequate amount.~~		Clarified procedural instructions
	• Schedule the ~~follow up~~ visit and advise the patient:	• Schedule the **next** visit**, reiterate dosing instructions**, and advise the patient: □ **NOT to take investigational product on the morning of the next visit, and** □ **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** □ **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted**.	Clarify study procedures.
9.7.12, Every 3 Months after Week 48	9.7.1~~3~~ Patients who have completed their 48-week double-blind treatment period will continue double blind treatment until all randomized patients have completed their ~~participation in the primary~~ treatment period and the database is locked…. and should not exceed the indicated maximal dose and frequency indicated for their CP category.	**9.7.11. Every 3 Months after Week 48** **<u>Quarterly</u>** • **Verify that the patient has fasted for at least 8 hours.** – **Record fasting status in the source and eCRF** – **If the patient reports having eaten within 8 hours, document accordingly in the source and**	Clarified dispensing instructions.

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	~~Patients will then have the option to continue into an open-label LTSE.~~	**eCRF and remind the patient that fasting is required prior to all study visits, but water is permitted.** • **Perform a physical examination, including smoking and alcohol consumption history, and current habits for both.** • **Review and record any non-study related medical or surgical treatment procedures and any medically relevant HCP or non-HCP related office visits that have occurred since the previous study visit.** • **Assess and record vital signs (oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Perform assessments for calculation of CP Score (Section 14.1.1).** • **Administer Quality of Life and Patient questionnaires (see Section 13.2.6).** • **Assess investigational product compliance, perform investigational product accountability.** • **Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed.** • **Assess for dose titration, if eligible (refer to Section 7.3).**	

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		• **Perform urinalysis (dipstick)** • **Perform a urine-based β-hCG pregnancy test in females of childbearing potential.** • **Obtain blood samples for** – **Serum chemistry, hematology, and coagulation** • **Schedule the next visit, reiterate dosing instructions, and advise the patient:** – **NOT to take investigational product on the morning of the next visit, and** – **To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and** • **To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.** **Patients will complete a TE/ELF (HA, P3NP and TIMP 1) and ultrasound (for HCC surveillance) assessment, every 6 months (±2 weeks) after Week 48.** **ECG will be done yearly (±2 weeks) after Week 48.**	
9.7.13, End of Study/Early Termination Procedures for Patients that Withdraw from Investigational Product or	9.1.14; End of ~~Treatment~~/Early Termination Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent … Patients who discontinue investigational product before are expected to continue … EOT/ET procedures will be required whenever patients discontinue treatment with investigational product	9.7.1**2**. . End of **Study**/Early Termination/**End of Treatment** Procedures for Patients that Withdraw from Investigational Product or Withdraw Consent … Patients who discontinue investigational product **before Week 48** are expected to continue ... EOT (when subject discontinues investigational product)/ET procedures will be required whenever patients discontinue treatment with investigational product (**Table 1, Section 9.7.10**)	Clarified procedures.

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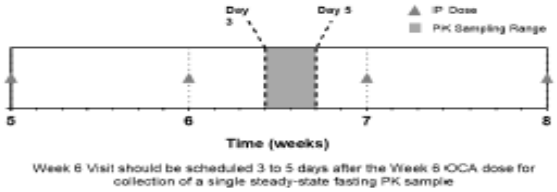
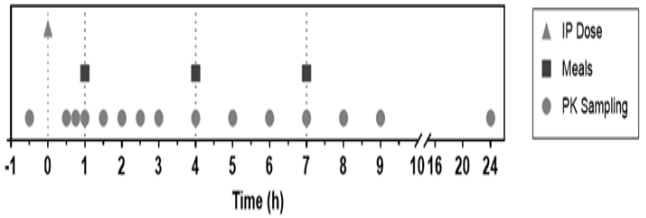
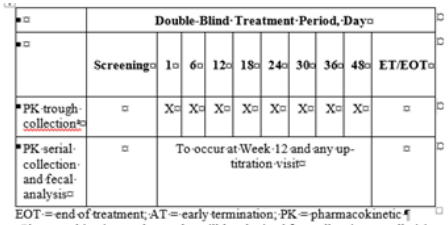
Withdraw Consent	When a patient discontinues investigational product ~~but~~ continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. (Insertion)	When a patient discontinues **or interrupts** investigational product **and** continues with regularly scheduled study visits, the EOS Visit will be completed as the patient's final study visit. **EOT and EOS visits are encouraged but at no time will a missed EOT or EOS visit be considered a protocol deviation.**	
9.7.13, Table 5, row 5	~~Treatment Interruption Interrupted RetainedRegular Visit Schedule Complete as close as possible to last dose of investigational product Complete at final study visit~~	Deleted	Removed to reduce confusion
10.3, Investigational Product Storage	~~Investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15ºC to 25ºC.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical studies are to be shipped and stored at 15°C to 25°C. Temperature excursions within the range of 2°C and 30°C for no more than a 6-month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20°C to 40°C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.**	Updated storage conditions per the Investigator's Brochure.
12, 12.1, Pharmacokinetic Blood Sampling	~~Subjects~~ with at least one PD assessment after dosing will be included in the combined PK/PD analyses Serial and ~~trough~~ PK assessments will be performed in all patients participating in the study. ~~At each visit~~, patients will provide…	**Patients in the PK Population** with at least one PD assessment after dosing will be included in the combined PK/PD analyses Serial and **fasting** PK assessments will be performed in all patients participating in the study. **At Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48**, patients will provide…	Specific dates are required to obtain optimum PK results

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	(Insertion)	**Week 6 visit should occur 3, 4, or 5 days after the Week 6 dose, (eg if the Week 6 dose of drug is taken on a Sunday, the patient should come in for the Week 6 visit between Wednesday and Friday [Figure 2]).**	
	(Insertion) …serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose…	**Figure 2: Week 6 Sampling Schedule**  Week 6 Visit should be scheduled 3 to 5 days after the Week 6 OCA dose for collection of a single steady-state fasting PK sample **IP = investigational product; PK = pharmacokinetic** **At Weeks 12, 18, 24, 30, and 48,** Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5**,** 6, **7, 8, 9 and 24 hours postdose (Figure 3) for all patients. The patient will be given the option to return** to the **clinic the following morning for the 24-hour postdose sample or samples can be obtained by a home health care designee. The home health care agency must be advised one week in advance of the appointment.**	Added diagram and language to clarify PK sampling procedures.
	(Insertion)	**Figure 3: Pharmacokinetic Sampling Schedule**  At meal timepoints, meals are consumed immediately after the collection of the PK sample **OCA = obeticholic acid; PK = pharmacokinetic**	Added diagram and language to clarify PK sampling procedures.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
12.1, Pharmacokinetic Blood Sampling	~~Table 7: Pharmacokinetic Sampling Schedule~~  Double Blind Treatment Period, Day Screening | 1 | 6 | 12 | 18 | 24 | 30 | 36 | 48 | ET/EOT PK trough collection[a] | X | X | X | X | X | X | X | X PK serial collection and fecal analysis | To occur at Week 12 and any up-titration visit EOT = end of treatment; AT = early termination; PK = pharmacokinetic [a] Pharmacokinetic trough samples will be obtained from all patients at all visits prior to dose administration. [b] Serial PK assessments will be performed in all patients at Week 12. Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible and uptitrated their dose. Sample collection for fecal analysis will occur concurrent serial PK sampling visits only.		Replaced with other Figures 2 and 3.
	During the ~~double blind~~ treatment period and ~~double blind LTSE:~~ • Pharmacokinetic ~~trough~~ samples will be obtained from all patients at all visits prior to dose administration in accordance with ~~Table 7~~. • Serial PK assessments will be performed in all patients ~~at Week 12~~. ~~Thereafter, PK assessments will be conducted at every titration visit in those patients who were eligible~~ and ~~uptitrated their dose~~. ~~Sample collection for fecal analysis will occur concurrent with serial PK sampling visits only.~~	During the treatment period: • Pharmacokinetic **fasting** samples will be obtained from all patients at **Weeks 6, 12, 18, 24, 30, 36, and 48** prior to dose administration in accordance with **Figure 3**. • Serial PK assessments will be performed in all patients **at Weeks 12, 18, 24, 30, and 48.**	Clarify PK sampling and collection procedures.
12.2, Processing and Handling of Pharmacokinetic Samples	The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site and in a separate document before the study is initiated.	The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site **and home health care company** in a separate document before the study is initiated.	Added option of using home health care service.
13, Assessment of Safety	~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.~~ ~~Safety will be assessed in terms of AEs. All AEs, whether observed by the investigator, reported by the patient, noted from laboratory findings, or identified by other means, will be recorded from the time the patient signs his/her consent~~	deleted	Safety information updated to match Protocol 747-302.

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td></td><td>~~form (s)until the patient completes study participation (final Follow Up Visit).~~
~~Recording AEs/SAEs in the electronic data capture (EDC) system is the method for reporting AEs/SAEs. It is therefore imperative, that AEs/SAEs are recorded into the EDC.~~</td><td></td><td></td></tr>
<tr><td rowspan="2">13.1.1.3. Treatment-Emergent Adverse Event</td><td>13.1.1.~~2~~
~~A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.~~</td><td>Moved to Section 13.1.3. Recording Adverse Event Severity</td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>~~Table 9: Severity of Adverse Events~~
<table><tr><th>Grade</th><th>Clinical Description of Severity</th></tr><tr><td>~~1=Mild~~</td><td>~~Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.~~</td></tr><tr><td>~~2=Moderate~~</td><td>~~Minimal, local or noninvasive intervention indicated, or limiting age-appropriate instrumental activities of daily living.~~</td></tr><tr><td>~~3=Severe~~</td><td>~~Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.~~</td></tr></table></td><td>Table 9: Severity of Adverse Events
<table><tr><th>Grade</th><th>Clinical Description of Severity</th></tr><tr><td>1=Mild</td><td>Causing no limitation of usual activities; the patient may experience slight discomfort.</td></tr><tr><td>2=Moderate</td><td>Causing some limitation of usual activities; the patient may experience annoying discomfort.</td></tr><tr><td>3=Severe</td><td>Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain.</td></tr></table></td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.3.1. Severity of Pruritus (as an Adverse Event)</td><td>~~To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used for AE reporting. As pruritus is a patientive symptom, clinical judgment should be used to determine its severity and management Table 10~~
Table 10 deleted.</td><td></td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.4.1. Reporting of Adverse Events</td><td>(Insertion)</td><td>…. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.</td><td>Safety information updated to match Protocol 747-302.</td></tr>
<tr><td>13.1.4.2. Reporting of</td><td>~~• Telephone:~~ PPD
If an SAE is reported by ~~telephone or~~ fax, …</td><td>If an SAE is reported by fax, …</td><td>Number no longer in use.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
Serious Adverse Events			
13.1.5.1. Potential Clinical Outcome Events	~~The events listed below will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events. These events will be evaluated by an Adjudication Committee (described in Section 15.9) to confirm if they meet the criteria to be considered Clinical Outcome Events.~~ ~~Potential Clinical Outcome Events:~~ ~~Hospitalization for clinical complications of cirrhosis.~~ ~~Given that the Potential Clinical Outcome Events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously report suspected Potential Clinical Outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a "potential study event" on the Adverse Event eCRF and will be submitted for adjudication to the Adjudication Committee as described in Section 15.9.~~		Safety information updated to match Protocol 747-302.
13.1.7. Notification of Post-Treatment SAEs for Patients Who Continue in the Study	13.1.7. Notification of Post-~~Study~~ SAEs ~~If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section 13.1.4.2~~	13.1.7. Notification of Post-**Treatment** SAEs **for Patients Who Continue in the Study** **Post-treatment SAEs that occur in patients who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.** **SAEs that occur in patients who discontinue investigational product, initiate treatment with commercially available Ocaliva, and remain in the study must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2**.	Safety information updated to match Protocol 747-302. Deleted text is already in Section 13.1.8.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
13.1.8. Notification of Post--Study SAEs	(Insertion)	**13.1.8. Notification of Post-Study SAEs** **All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.**	Safety information updated to match Protocol 747-302.
13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	~~13.1.8. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study~~ ~~Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2~~	Moved to 13.1.7	Safety information updated to match Protocol 747-302 9 (moved to 13.1.7).
13.1.10, Pregnancy and Follow-up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must ~~discontinue~~ investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing. ~~In the situation that the EDC is not functioning, the Medical Monitor should be notified by telephone. The investigator remains responsible for entering the pregnancy information into the EDC when the EDC becomes functional.~~	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must **interrupt treatment with** investigational product immediately (see Section) and the Sponsor must be notified within 24 hours of the Investigator's **awareness** of the pregnancy by completing the Pregnancy **CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to** PPD **or faxed to** PPD **.** **The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.** **The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The patient must have a negative pregnancy test before restarting investigational product. If a patient's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy**	Safety information updated to match Protocol 747-302.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		confirmed by a serum β-hCG test before restarting investigational product.	
13.2.2, Physical Examination	13.2.~~1~~ (Insertion)	13.2.**2** A basic physical examination… **Smoking and alcohol consumption history and current habits will be recorded**….	Clarified assessments
13.2.5, Laboratory Assessments	~~For visits that require fasting~~, the Investigator or designee will verify that the patient has fasted for at least 8 hours …	**At all visits (except screening),** the Investigator or designee will verify that the patient has fasted for at least 8 hours…	Clarified visit procedures
	Blood samples for serum chemistry, coagulation, and hematology will be collected at ~~every visit~~…	Blood samples for serum chemistry, coagulation, and hematology and **urine samples** will be collected at **visits**…	Clarified what samples will be collected.
13.2.5, Laboratory Assessments, Table 9		Added the following labs: • Serum Chemistry – **CPK, TFT (TSH, free T3 and free T4)** • Urinalysis **(dipstick)** – **Pregnancy** • Noninvasive measurement… – **ELF (HA, P3NP, and TIMP-1), TE**	Updated lab tests to be performed.
	~~Biomarkers~~ of ~~Hepatic Fibrosis and/or~~ Inflammation; IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK 18 M30, ~~and others as determined during course of study~~	Markers of Inflammation; IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30	Clarified assessments
	~~Genetics; DNA including single nucleotide polymorphisms that may be involved in PBC; RNA~~	deleted	No longer doing this analysis.
13.2.5, Laboratory Assessments	(Insertion)	**PD markers**: C4, **FGF-19 and plasma bile acids**	Added new row

<table>
<tr><th>Section</th><th>Original Text (Version 1, 20 Dec 2016)</th><th>Revised Text (Version 2, 22 May 2017)</th><th>Key Change</th></tr>
<tr><td>13.2.5, Laboratory Assessments</td><td>(Insertion)</td><td>Laboratory reference ranges for the study will be based on the laboratory vendor range.</td><td>Added to satisfy PMR request.</td></tr>
<tr><td>14.1.1, Child-Pugh Score, Table 10</td><td><table>
<tr><th>Factor</th><th>Units</th><th colspan="3">Points</th></tr>
<tr><th></th><th></th><th>1</th><th>2</th><th>3</th></tr>
<tr><td><s>Serum bilirubin</s></td><td><s>µmol/L</s></td><td><s><3 5</s></td><td><s>35 50</s></td><td><s>>50</s></td></tr>
<tr><td><s>Serum albumin</s></td><td><s>g/L</s></td><td><s>>3 5</s></td><td><s>28 35</s></td><td><s><28</s></td></tr>
<tr><td>Hepatic encephalopathy</td><td></td><td><s>No</s></td><td></td><td></td></tr>
</table></td><td>Deletion

Encephalopathy now 0</td><td>Simplified CP scoring procedure.</td></tr>
<tr><td>14.2.1, Markers of Inflammation, Apoptosis and Necrosis</td><td>Blood samples for analytes including hs-CRP, IgM, TNF-α, and cytokeratin-18, neoepitope M30.</td><td>Blood samples for analytes including IL-6, hs-CRP, IgA, IgG, IgM, TNF-α, and cytokeratin-18, neoepitope M30.</td><td>Added additional markers.</td></tr>
<tr><td>15.4, Safety Analyses</td><td>No inferential comparison <s>of safety endpoints</s> will be performed. <s>All</s> safety <s>comparisons will be descriptive.</s></td><td>No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.</td><td>Clarified statistical analyses.</td></tr>
<tr><td>15.4.3, Adverse Events of Special Interest</td><td>… The <s>quartiles, including</s> the median <s>time-to-event</s> and <s>their respective</s> 2-sided 95% CIs, will be presented. <s>KM estimates will be plotted</s> as <s>a “survival curve” for each treatment group.</s></td><td>… The tabulation will include the KM estimate methodology using 25th, 50th (median), and 75th percentiles of the medians and corresponding with associated 2-sided 95% confidence intervals (CIs), if the medians can be estimated as well as percentage of censored observations.</td><td>Clarified statistical analyses.</td></tr>
<tr><td>15.5, Efficacy Analyses, 4th paragraph</td><td>… The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 95% CI of the difference will also be presented. <s>No formal hypothesis testing will be performed.</s></td><td>The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square (LS) means, standard errors (StdErr), and 2-sided 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the StdErr of the difference, and 2-sided 95% CI of the difference will also be presented</td><td>Clarified statistical analyses.</td></tr>
</table>

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
15.6, Additional Efficacy Analyses	The following clinical ~~outcomes~~ will be captured in the study: • All cause ~~mortality~~ • Liver related death • Liver transplant • Variceal bleed • Hepatic encephalopathy • Bacterial peritonitis • ~~Ascites~~ • ~~Hepatocellular carcinoma~~	The following clinical **endpoints** will be captured in the study : • **Time to death** (all-cause) • **Time to** liver-related death • **Time to hepatic failure** leading to liver transplant • **Model of end stage liver disease (MELD) score ≥15 (for patients with MELD ≤12 at baseline)** • **Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:** – **Time to variceal bleed** – **Time to hepatic encephalopathy (as defined by a West Haven score of ≥2)** – **Time to spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)** • **Time to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).** The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-	Clarified statistical endpoints.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
		sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata. **In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of hepatocellular carcinoma (HCC) will be summarized by treatment group using the same methods as defined above.**	
18.3, Written Informed Consent	(Insertion)	**The Investigator(s) must maintain the original, signed ICF. A copy of the ICF must be given to the patient.**	Updated language.
21, List of References	(Insertion)	**Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014 Sep;61(3):642-59.** **Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007 Mar;45(3):797-805.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-72.**	Added new references
Appendix A, List of Study 747-401 Outcome Events	~~Some of the specified clinical endpoints will also by definition (see Section 13.1) qualify as Serious Adverse Events (SAEs). The sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 13.1.4). The Sponsor is responsible for regulatory reporting of SAEs including expeditious reporting of SAEs that are considered related to the investigational product and considered Unexpected by regulatory standards as defined in the Investigational Brochure.~~		This is covered in the main text.

Section	Original Text (Version 1, 20 Dec 2016)	Revised Text (Version 2, 22 May 2017)	Key Change
	~~The Sponsor may consider the following lists of events to be exempt from expeditious regulatory reporting but will continue to report them in a non-expeditious manner:~~ ~~Potential Clinical Outcome Events:~~ ~~Liver related events resulting in death~~ ~~Hepatic failure leading to liver transplant~~ ~~Variceal bleed~~ ~~Hepatic encephalopathy~~ ~~Spontaneous bacterial peritonitis~~ ~~Ascites~~ ~~Hepatocellular carcinoma~~		

APPENDIX B. SUMMARY OF CHANGES: PROTOCOL 747-401 VERSION 3 (DATED 04 JAN 2018)

Protocol 747-401 was revised to include the following information:

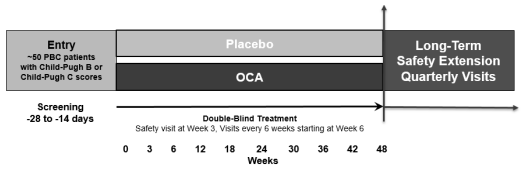
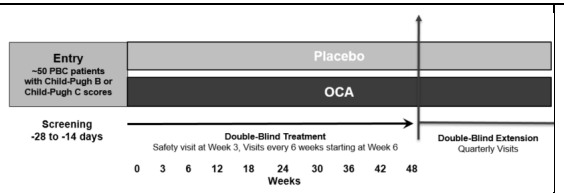
- The Introduction was revised to highlight the need for close monitoring specifically in patients with clinical evidence of hepatic decompensation and other complications due to advanced cirrhosis. Reference is made to sections describing specific criteria for investigational product adjustment, interruption, or discontinuation based on adverse events or laboratory values. This language also emphasizes the need for careful observation and evaluation of the entire clinical picture over and above system-generated alerts and flags for lab values.
- Dosing regimens were updated to modify dosing to one regimen for patients with moderate and severe hepatic impairment (eg, same for CP-B and CP-C), not to exceed 10 mg twice weekly, to align with label dosing guidelines. Titration is now only based on tolerability and not CP score.
- Reference to an option for open-label treatment was removed. An open-label extension will be considered only after review of blinded safety and PK data from the double-blind treatment period. For clarity, reference to the Long-Term Extension was changed to Double-Blind Extension; visits during this period remain the same.
- Protocol was updated with discontinuation criteria for decompensation events and biochemical thresholds. A plan for monitoring and drug-induced liver injury algorithm has been included to ensure careful monitoring and drug interruption/discontinuation. Analysis of decompensation events as adverse events of interest has been added. Additionally, “Close Observation” per FDA Guidance for Industry on Drug Induced Liver Injury” has been clearly defined in the protocol to ensure that patients who experience a potential DILI undergo a full evaluation.
- Guidance was added that patients should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as: pale-colored stools, urine color from pale to deep amber [dark], nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or the whites of eyes, and bruising easily.
- Guidance was added that the Investigator should contact the study Medical Monitor upon awareness when any signs and symptoms of hepatic decompensation are observed in any patient.
- Guidance was added for monitoring amylase and lipase levels in patients with suspected acute pancreatitis.
- Gallbladder assessments were added at Screening or Day 1.

Summary of Changes

The following revisions were made to the protocol in Protocol Version 3. Revised and new text in Version 3 is indicated in bold font, and the text deleted from Protocol Version 2 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Sponsor's Approval of the Protocol	PPD PhD Vice President, Clinical Development Intercept Pharmaceuticals, Inc.	PPD PhD **Sr** Vice President, Clinical Development Intercept Pharmaceuticals, Inc.	Signatory's title changed.
Study Personnel Contact Information	~~Medical Monitor~~ ~~Primary Contact:~~ PPD ~~MD~~ ~~Medical Director, Pharmacovigilance,~~ ~~Intercept Pharmaceuticals, Inc. (Intercept)~~ ~~Telephone:~~ PPD ~~Email:~~ PPD SAE Fax: PPD SAE Email: PPD	**Medical Monitor** **Primary Contact:** PPD **DO, MSPH** **Senior Medical Director, Intercept Pharmaceuticals, Inc. (Intercept)** PPD **Secondary Contact:** PPD **MD** **Senior Medical Director, Intercept Pharmaceuticals, Inc. (Intercept)** PPD **24-Hour Telephone:** PPD SAE Fax: PPD SAE Email: PPD	Change in personnel.
Synopsis, Study Period; Section 7.1.3, Study Duration	Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). ~~Patients will then be given the option to go on open-label treatment.~~	Study Period: Patients will receive double-blind treatment for at least 48 weeks. Patients who have completed their 48-week double blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). **An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.**	An open-label extension will only be considered only after review of blinded safety and PK data from the double-blind treatment period.
Synopsis, Phase of Development	Phase 4	Phase 4**: US, Canada, and the EU** **Phase 3b: All other regions**	Study is only considered a Phase 4 in regions where Ocaliva has received regulatory approval.

Synopsis, Additional Objectives; Section 6.3, Additional Objectives	Additional Objectives: • To evaluate the effect of OCA treatment compared to placebo on: ~~– Markers of inflammation~~ – Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score) – Noninvasive measurement of liver stiffness (transient elastography [TE])	Additional Objectives: • To evaluate the effect of OCA treatment compared to placebo on: – Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™ score) – Noninvasive measurement of liver stiffness (transient elastography [TE])	Samples were removed to simplify the study design.
Synopsis, Double-Blind Treatment Period; Section 7.1, Overall Study Design	Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. ~~At each visit (except screening and Week 3), fasting~~ PK assessments will be performed in all patients participating in the study~~.~~ Serial PK sampling will be performed at Week 12, 18, 24, 30, and 48. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. ~~Patients will then be given the option to go on open-label treatment.~~	Double-Blind Treatment Period: During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. **Titration may be considered as early as the Week 12 Visit. Fasting** PK assessments will be performed in all patients participating in the study **on Day 1, Week 6, and Week 36.** Serial PK sampling **(which also includes a fasted PK assessment)** will be performed at Week 12, 18, 24, 30, and 48. Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their 48-week treatment period and the database for that period is locked. **An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.**	Clarification for sites needed to clarify Fasted and Serial PK assessment timepoints. An open-label extension will only be considered only after review of blinded safety and PK data from the double-blind treatment period.

Synopsis, Study Design Diagram; Section 7.1.1 Study Design Diagram	 OCA = obeticholic acid, PBC = primary biliary cholangitis Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability ~~and CP score~~. Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.	 OCA = obeticholic acid, PBC = primary biliary cholangitis Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability. Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.	Clarification of extension period needed to ensure it is not confused with an open-label extension.

<table>
<tr>
<td>Synopsis, Dosing Regimen; Section 7.3 Planned Dosing Regimen</td>
<td>…
Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on ~~safety and~~ tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.
~~Patients with CP-B may titrate to a maximum dose of OCA 5 mg once daily.~~
~~Patients with CP-C may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.~~
~~If, during the course of the study, a patient transitions from CP-B to CP-C, or vice versa, the maximal dose for the new CP classification would apply.~~
Planned OCA or Matching Placebo Dosing Regimen ~~by Child-Pugh Score~~
<table>
<tr><td></td><td colspan="2">Child-Pugh B (Moderate Hepatic Impairment)</td><td colspan="2">~~Child-Pugh C (Severe Hepatic Impairment)~~</td></tr>
<tr><td></td><td colspan="2">Treatment Group</td><td colspan="2">~~Treatment Group~~</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td><td>~~OCA~~</td><td>~~Placebo~~</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo</td><td>~~5 mg once weekly~~</td><td>~~matching placebo~~</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo</td><td>~~5 mg twice weekly[b]~~</td><td>~~matching placebo~~</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo</td><td>~~10 mg twice weekly[b]~~</td><td>~~matching placebo~~</td></tr>
</table>
</td>
<td>…
Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose.
Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.
Planned OCA or Matching Placebo Dosing Regimen
<table>
<tr><td></td><td colspan="2">Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)</td></tr>
<tr><td></td><td colspan="2">Treatment Group</td></tr>
<tr><td></td><td>OCA</td><td>Placebo</td></tr>
<tr><td>Starting Dose (Day 1)</td><td>5 mg once weekly</td><td>matching placebo once weekly</td></tr>
<tr><td>Titration 1[a]</td><td>5 mg twice weekly[b]</td><td>matching placebo twice weekly[b]</td></tr>
<tr><td>Titration 2[a]</td><td>10 mg twice weekly[b]</td><td>matching placebo twice weekly[b]</td></tr>
</table>
[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.</td>
<td>Per FDA request to align dosing with label dosing guidelines for CP-B and CP-C patients.</td>
</tr>
</table>

	~~Titration 3[a]~~	~~5 mg once daily~~	~~matching placebo~~	~~NA~~	~~NA~~

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability ~~and/or changes in Child-Pugh Score at any time during the study.~~

[b] Dosing per the twice weekly schedule must be at least 3 days apart.

~~Over the course of the study, a patient's CP category may change. When a patient demonstrates a change in CP category, dosing should be reassessed and modified if appropriate. Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply. If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen should be followed.~~

~~Maximum Dose for OCA or Matching Placebo for Changes in Child-Pugh Category~~

~~Original Status~~	~~New Status[a]~~		
	~~Child-Pugh A~~	~~Child-Pugh B~~	~~Child-Pugh C~~
~~Child-Pugh B~~	~~*No change*~~	~~*No change*~~	~~10 mg twice weekly~~
~~Child-Pugh C~~	~~5 mg once daily~~	~~5 mg once daily~~	~~*No change*~~

~~[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for the planned dosing regimen.~~

~~[b] Dosing per the twice weekly schedule must be at least 3 days apart.~~

Synopsis, Key Inclusion Criteria; Section 8.2, Patient Inclusion Criteria	3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening ~~(ie, within 14 days before the first dose of investigational product):~~	3. Satisfy the criteria of the modified CP classification for hepatic impairment during Screening	Correction

<table>
<tr><td>Synopsis, Key Exclusion Criteria; Section 8.3, Patient Exclusion Criteria</td><td>4. ~~Hepatic~~ encephalopathy (as defined by a West Haven score of ≥2)</td><td>4. Current hepatic-encephalopathy (as defined by a West Haven score of ≥2)</td><td>Correction</td></tr>
<tr><td>Synopsis, Key Exclusion Criteria</td><td>5. History or presence of other concomitant liver diseases including:
• Hepatitis C virus infection and RNA positive
• Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B antigen negative) may be included in this study after consultation with the medical monitor</td><td>5. History or presence of other concomitant liver diseases including:
• Hepatitis C virus infection and RNA positive
• Active hepatitis B infection; however, patients who have seroconverted (hepatitis B surface antigen and hepatitis B e antigen negative) may be included in this study after consultation with the Medical Monitor</td><td>Correction</td></tr>
<tr><td>Synopsis, Duration of Treatment</td><td>Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). ~~Patients will then be given the option to go on open-label treatment.~~</td><td>Patients who have completed their 48-week double blind treatment period will continue double blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years). An open-label extension study in which all patients receive OCA will be considered following review of blinded safety and PK data.</td><td>An open-label extension will only be considered only after review of blinded safety and PK data from the double-blind treatment period.</td></tr>
<tr><td>Synopsis, Criteria for Evaluation; Section 11, Overview of Assessments, Table 7</td><td>
<table>
<tr><th>Secondary Objectives</th><th>Assessments</th></tr>
<tr><td>Changes in risk scores</td><td>Changes in MELD and in CP score and components of the CP score</td></tr>
<tr><td>Changes in liver biochemistry and hepatobiliary damage</td><td>Total and direct bilirubin, ALP, ALT, AST, GGT, INR, creatinine, albumin, platelets</td></tr>
<tr><td>PD parameters</td><td>FGF-19, C4, and plasma bile acids</td></tr>
<tr><th>Additional Objectives</th><th>Assessments</th></tr>
<tr><td>~~Markers of inflammation~~</td><td>~~IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30~~</td></tr>
<tr><td>Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis</td><td>TE and ELF (HA, P3NP, and TIMP-1)</td></tr>
</table>
</td><td>
<table>
<tr><th>Secondary Objectives</th><th>Assessments</th></tr>
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<tr><td>PD parameters</td><td>FGF-19, C4, and plasma bile acids</td></tr>
<tr><th>Additional Objectives</th><th>Assessments</th></tr>
<tr><td>Noninvasive measurements of liver fibrosis, liver stiffness and cirrhosis</td><td>TE and ELF (HA, P3NP, and TIMP-1)</td></tr>
</table>
</td><td>Risk score assessment clarified.

Markers of inflammation were removed to simplify the study design.</td></tr>
</table>

<table>
<tr>
<td>Section 14.1.1, Child-Pugh Score</td>
<td>
<table>
<tr><th rowspan="2">Factor</th><th rowspan="2">Units</th><th colspan="3">Points</th></tr>
<tr><th>1</th><th>2</th><th>3</th></tr>
<tr><td rowspan="2">Serum bilirubin</td><td>µmol/L</td><td><3~~5~~</td><td>3~~5~~-50</td><td>>50</td></tr>
<tr><td>mg/dL</td><td><2.0</td><td>2.0-3.0</td><td>>3.0</td></tr>
</table>
</td>
<td>
<table>
<tr><th rowspan="2">Factor</th><th rowspan="2">Units</th><th colspan="3">Points</th></tr>
<tr><th>1</th><th>2</th><th>3</th></tr>
<tr><td rowspan="2">Serum bilirubin</td><td>µmol/L</td><td><34</td><td>34-50</td><td>>50</td></tr>
<tr><td>mg/dL</td><td><2.0</td><td>2.0-3.0</td><td>>3.0</td></tr>
</table>
</td>
<td>Error correction</td>
</tr>
<tr>
<td>Synopsis, Safety Analyses; Section 15.4, Safety Analysis</td>
<td>Safety analyses will be conducted using the Safety population. Safety data, including AEs, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group.</td>
<td>Safety analyses will be conducted using the Safety population. Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vital signs, electrocardiogram, and clinical laboratory results will be summarized by treatment group.</td>
<td>Per FDA request</td>
</tr>
<tr>
<td>Synopsis, Additional Efficacy Analyses; Section 15.6, Additional Efficacy Analyses</td>
<td>Analyses of changes in liver stiffness and ELF~~, cytokeratin and TIMP-1, and markers of inflammation~~ will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.</td>
<td>Analyses of changes in liver stiffness (TE) and liver fibrosis (ELF [HA, P3NP, and TIMP-1]), will be summarized and analyzed using the same methodology specified for the secondary analyses of change in bilirubin.</td>
<td>Correction</td>
</tr>
<tr>
<td>Synopsis, Sample Size Justification; Section 15.2, Determination of Sample Size</td>
<td>To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. ~~Ten~~ patients on placebo will be included as a comparator. An additional 20 patients ~~will~~ be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized.</td>
<td>To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. A total of 30 patients is adequate with 10 patients on placebo to be included as a comparator and 20 patients on OCA. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized in a 1:1 ratio to 1 of the 2 treatment groups: Placebo and OCA.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>Section</td>
<td>Original Text (Version 2)</td>
<td>Revised Text (Version 3)</td>
<td>Key Change
Reasons /
Justification for Change</td>
</tr>
</table>

Section 5.1, Overview of Disease State and OCA	In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication~~.~~	In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval for OCA (marketed as Ocaliva), for the treatment of patients with PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication**, and in May 2017 Ocaliva received approval from Health Canada. Study 747-401 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC (ie, in the US, Canada, and the EU). In all other regions, this study is considered Phase 3b.**	Ocaliva has been approved in Canada since last version of protocol. Study is only considered a Phase 4 in regions where Ocaliva has received regulatory approval.
Section 5.3, Clinical Development of Obeticholic Acid	As of ~~31 Jan~~ 2017, approximately ~~2186 patients~~ have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~525~~ patients had PBC, ~~686~~ patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, ~~52~~ patients had primary sclerosing cholangitis (PSC), and ~~5~~ patients had biliary atresia.	As of **13 Oct** 2017, approximately **2690 subjects** have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **552** patients had PBC, **1141** patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, **73** patients had primary sclerosing cholangitis (PSC), and **6** patients had biliary atresia.	Updated exposure numbers available

5.4.2, Rationale for Obeticholic Acid Dose and Duration	Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3). ~~The dosing regimen in this study follows the FDA-approved prescribing information, with the exception of the maximum allowed dose in patients with moderate impairment. While the prescribing information allows for a maximum dose of 10 mg twice weekly for patients with moderate impairment, the protocol allows for a maximum dose of 5 mg once daily. The choice of 5 mg once daily is supported by the estimated steady-state liver and plasma exposure of total OCA for patients with moderate hepatic impairment receiving a 5 mg once daily dose relative to healthy patients receiving a 10 mg dose. A maximum allowed dose of 5 mg once daily in patients with moderate hepatic impairment is estimated to achieve liver exposure similar to non-hepatically impaired patients receiving a 10 mg daily dose and maximize efficacy in this patient population.~~	Therefore, the current FDA-approved prescribing information for OCA includes a modified dosing regimen in patients with moderate and severe hepatic impairment that is designed to achieve liver exposures in these patients that would be similar to non-hepatically impaired patients through initiation at a lower dose (5 mg OCA once-weekly) followed by gradual up-titration (Section 7.3).	Text no longer applicable since all dosing regimens will follow FDA-approved prescribing information.

Section 5.5, Importance of Monitoring Disease Progression	New Section	**Given PBC is a chronic, progressive liver disease, it is important that patients with PBC are closely monitored to ensure early identification of decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve patient oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual patients to determine on an ongoing basis the totality of a patient's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring.** **Patients will be monitored for potential hepatic injury and/or decompensation. Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 8.4 and Section 7.6. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.**	Language added to generate Investigator awareness of the disease progression trajectory and unpredictable nature of progression in patients at high risk, as well as incorporation of language regarding altered bile acid and OCA PK and drug exposure in patients with hepatic impairment and the need for close vigilance to identify potential liver toxicity or decompensation.

Section 5.6, Summary of Known Potential Risks with Investigational Product	~~The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy patients, but with a much lower frequency than that observed in patients with PBC.~~ ~~Consistent with the dose-limiting hepatic toxicities observed in the non-clinical studies and the chemical characteristics of OCA as a bile acid and detergent, dose-related but reversible and asymptomatic increases in ALT and AST were observed in healthy volunteers treated with multiple doses of OCA starting at the 100 mg dose (Study 747-102).~~ ~~In patients with chronic liver disease such as PBC, hepatobiliary findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed. These findings were seen more frequently with doses of OCA 10 mg once daily to OCA 50 mg once daily (up to 5x the highest recommended dose). In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.~~ ~~Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDLc) and an increase in low density lipoprotein (LDLc). Notably, in patients with PBC, the decrease in mean HDLc levels occurred early and stabilized within 3 months after which time levels generally remained constant over the course of treatment. The average levels of HDLc remained within normal limits. Commensurate with decreases in HDLc, decreases in total cholesterol were observed in patients with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA treated patients with the exception of a modest transient and early rise after initiation of treatment.~~ ~~Based on previous PK and short-term studies in patients with hepatic impairment, increased systemic exposure was not associated with an apparent change in the safety profile of OCA as assessed by the incidence and severity of AEs or by changes in clinical laboratory tests. Hepatotoxicity has been associated with increased liver concentrations of OCA. Hepatic impairment does not~~	**The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk.** **<u>Clinical Data</u>** **In two Phase 2 studies and a Phase 3 study evaluating OCA in the treatment of subjects with PBC, hepatic adverse events were observed in subjects receiving doses of OCA ranging from the maximum approved dose of 10 mg once daily to 50 mg (5 times the highest recommended dose).** **Recent safety findings in NASH clinical trials include 2 cases of hepatic decompensation reported as SUSARs, 1 of which resulted in death. Both cases involved numerous confounding factors that make evaluation of association with treatment difficult. Details for both events are provided in the Investigator's Brochure Addendum 1 to Version Number: 16 (31 March 2017), Effective Date: 02 October 2017.** **The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease.** **Changes in lipid profiles have also been observed with OCA dosing, including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further.** **Independent data monitoring committees (DMCs) have performed detailed reviews of several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by**	Updated in relations to other revisions made per FDA request.

	~~affect the ability of OCA to activate FXR in the intestine and the liver.~~ Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.		**treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification.** **Post-Marketing Cases in PBC** **As of September 2017, greater than 3000 patients have received Ocaliva® in the post-marketing setting. In patients with moderate to severe hepatic impairment (Child-Pugh B and C), liver decompensation, liver failure, and death have been reported when Ocaliva was dosed up to 7 times the recommended once weekly starting dose for such patients. Based on the initial medical assessment of these cases, which included patients having undergone liver transplant, there was insufficient evidence suggesting a causal relationship between higher than recommended dosing and the reported adverse events. However, Intercept Pharmaceuticals, Inc. (the Sponsor) continues to assess the potential association between adverse events, including deaths, and the higher than recommended dosing of Ocaliva observed in PBC patients with moderate to severe hepatic impairment (Child-Pugh B and C) through ongoing post-marketing pharmacovigilance activities.** **Signs and symptoms reported in patients experiencing liver-related adverse events who received Ocaliva include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice, and liver decompensation.** Refer to the IB for additional information regarding the known potential risks with the investigational product.	
Section 7.1.2, Schedule of Study Procedures, Table 1	Treatment Period (Weeks)	~~Long-Term Safety~~ Extension	**Double-Blind** Treatment Period (Weeks)[b]	**Double-Blind** Extension	Clarification

Section 7.1.2, Schedule of Study Procedures, Table 1	Insertion	**Week 42 Visit added with assessments to match Week 3 Visit plus assesments to assess for dose titration and dispense IP.**	Correction
Section 7.1.2, Schedule of Study Procedures, Table 1, Screening, Day 1	Insertion	**Gallbladder assessment (ultrasound)**	Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications).
	Insertion	Footnotes added r **If an ultrasound has been done within 12 months of Screening, and a report/adequate data are available, a pretreatment ultrasound at Screening is not required.** s **If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.**	
Section 7.1.2, Schedule of Study Procedures, Table 1	~~Markers of Inflammation: IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30~~	Deletion	Samples were removed to simplify the study design.
Section 7.1.2, Schedule of Study Procedures, Table 1	Insertion	**Amylase and Lipase: Sample to be collected if the patient experiences acute pancreatitis or cholecystitis.**	Per FDA request.
Section 7.1.2, Schedule of Study Procedures, Table 1	PK Fasting Collection *Removed for Weeks 12, 18, 24, 30, and 48/ET/EOS/EOT*	Deletion	Clarification for sites needed to clarify Fasted and Serial PK assessment timepoints. Serial PK is fasted, so indicating both types of assessments for these days was redundant.
Section 7.1.2, Schedule of Study Procedures, Table 1	Insertion	Footnote added to Serum Chemistry/Hematology/Coagulation l **MELD values will be calculated based on serum chemistry coagulation values at each visit.**	Clarification.
Section 7.4, Monitoring and Management of Potential Hepatic Injury and/or Disease Progression	New Section	**Given the chronic nature of PBC, it is important to monitor for potential hepatic injury, disease progression and/or hepatic decompensation. Child-Pugh and MELD scores will be reviewed at each visit where labs are drawn (Table 1). In addition, adverse events, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.2. Based on biochemical and clinical assessments, the investigational product**	Extensive safety monitoring and dosing adjustments, interruptions, or discontinuations are required given the elevated risk of decompensation and higher hepatic exposure to OCA in this population. It is important that Investigators construct an entire clinical picture, which includes

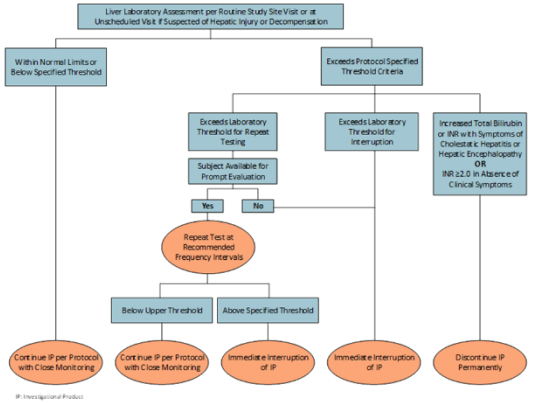
		may be interrupted or discontinued per criteria discussed in Section 7.4.2 and Section 7.4.3, and close monitoring procedures will be implemented (refer to Section 7.6).	not only rules based monitoring but careful evaluation of signs and symptoms of potential decompensation and diagnostic dilemmas.
Section 7.4.1, Signs and Symptoms of Potential Hepatic Injury or Decompensation	New Section	**Patients should be instructed to contact study personnel if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting** **<u>Signs and Symptoms of Hepatic Injury or Decompensation:</u>** • **Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark] (reflecting impaired bilirubin metabolism)** • **More general signs and symptoms of ascites and encephalopathy: confusion, swelling of the legs or abdomen** • **Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite** • **Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea for more than 4 days) and should be an indication for prompt investigational product interruption and complete patient evaluation** **<u>Other Symptoms:</u>**	Per FDA request.

		• **Worsening of renal function or likely dehydration** **<u>Healthcare Provider (HCP) Interactions:</u>** • **Visits to primary HCP or referral to any specialist for any new symptoms (other than ongoing care for stable comorbidities)** • **New medications or changes to current medications prescribed from HCP or any new over the counter medications or herbal supplements** • **Laboratory procedures or assessments performed by an HCP** **Signs and symptoms for potential hepatic injury or decompensation should be followed by (1) evaluation of liver biochemistry for suspected drug-induced liver injury (DILI) or potential hepatic decompensation (Section 7.4.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.4.3), (3) triggering of close monitoring or investigational product interruption/discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 13.1), and (5) contact with the Medical Monitor.**	
Section 7.4.2, Liver Biochemistry Assessments for Potential Hepatic Injury or Hepatic Decompensation	New Section	**Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of patients for potential hepatic injury or hepatic decompensation. These assessments will be performed at:** • **Each protocol-specified visit (Table 1)** • **Unscheduled visits as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered** **It is important that the laboratory assessments be completed as required and that the central**	Per FDA request.

laboratory be used for assessments whenever possible. In the event that a patient cannot return to the clinic for a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local lab is permissible at the discretion of the Investigator. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges.

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and, potentially, a complete patient evaluation (depending on the repeat result) are summarized in Table 3.

Figure 2: DILI Management Algorithm



DILI = drug-induced liver injury; IP = Investigational Product

NOTE Other laboratory criteria include: ALT, AST, total bilirubin, INR, and electrolytes (sodium).

Table 3 Liver Laboratory Criteria for Monitoring of Suspected Hepatic Injury or Potential Hepatic Decompensation and Criteria for Interruption or Discontinuation of Investigational Product

		It should be noted that it is difficult to recognize every potential marker of hepatic or renal deterioration. There is no substitute for good medical judgment. Investigators will be reminded to be cautious and mindful in their evaluation of patients' symptoms, signs, and laboratory results. However, for example, a single abnormal laboratory analyte result may be artefactual; accordingly, Investigators will be allowed to implement an alternate follow-up procedure if considered appropriate based on their medical judgement, but only after documented agreement with the Sponsor's Medical Monitor.	
7.4.3, Clinical Criteria for Monitoring for Potential Hepatic Decompensation	New Section	**Patients will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 4.** **Investigational product should be discontinued permanently if the patient received a liver transplant or experiences multi-organ failure as defined in Table 4, Part A. Patients should continue to return for scheduled study visits for safety follow up.** **Patients who experience other potential hepatic decompensation events defined in Table 4, Part B should be closely monitored until normalization or stabilization. Patients may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.** **Table 4 Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Interruption / Discontinuation of Investigational Product**	Per FDA request.
7.5, Dose Titration Criteria	Dose ~~Adjustment~~ Criteria Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns ~~or as a result of changes in a patient's CP Score~~. Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as	Dose **Titration** Criteria Dose titration may follow the scheduled dosing regimens described in Section 7.3 or occur due to tolerability concerns. Dose titrations may involve increases or decreases in dosing frequency and are dependent on tolerability (as assessed by a review of AEs and safety laboratory	Updates made to reflect titration for dosing per label dosing guidelines.

	assessed by a review of AEs and safety laboratory results). In general, down-titration may be done in response to tolerability concerns and can occur at any time. Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated ~~for each dosing regimen~~ as defined in Section 7.3. **Scheduled Dose Titration -** After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose ~~or dosing frequency~~ for patients may occur no earlier than 6 weeks following an up-titration. **Tolerability Dose Titration -** Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability) ~~**Dose Titration due to Change in CP Score** Over the course of the study, a patient's CP category may change. When a patient demonstrates a change in CP category (as assessed per Table 12), dosing should be reassessed and modified if appropriate (Table 2). Changes to the dosing regimen are not mandatory and should be based on clinical judgment and change in CP score. The titration steps for CP-B and CP-C patients are identical with exception of the maximum allowed dose. Therefore, if a patient changes CP class from B to C, or vice versa, the maximal dose for the new regimen will apply (Table 2). If a patient improves to CP-A during the study, the maximal CP-B dose will still apply. If a patient has not yet reached the maximal dose, the appropriate titration regimen (Table 2) should be followed.~~ ~~Table 3: Maximum Daily dose based on change in Child-Pugh Category~~	results). In general, down-titration may be done in response to tolerability concerns and can occur at any time. Up-titration will be done per protocol based on tolerability, as assessed by the Investigator based on response, or following resolution of a tolerability concern that previously led to down-titration. Up-titrations may only occur to the maximum dose and frequency indicated as defined in Section 7.3. Scheduled Dose Titration - After initiation of OCA or matching placebo, titration may be considered as early as the Week 12 Visit. Subsequent titrations in dose for patients may occur no earlier than 6 weeks following an up-titration. Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose as considered clinically appropriate (eg, tolerability).	

	~~Original Status~~ / ~~New Status[a]~~: ~~Child-Pugh A~~ / ~~Child-Pugh B~~ / ~~Child-Pugh C~~ ~~Child-Pugh B~~: ~~*No change*~~ / ~~*No change*~~ / ~~10 mg twice weekly~~ ~~Child-Pugh C~~: ~~5 mg once daily~~ / ~~5 mg once daily~~ / ~~*No change*~~ ~~[a] Once a patient begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.3 .~~ ~~[b] Dosing per the twice weekly schedule must be at least 3 days apart.~~ ~~CP Scores will be calculated at all study visits (except Week 3). While PBC-specific versions of CP scores are available, this study will use the standard calculation (Pugh 1973, Lucey 1997). All associated visit data (including central laboratory results) should be entered into the electronic case report form (eCRF) in a timely fashion to confirm that the patient's CP Score has not changed. If a change in CP Score is observed independent of a study visit, the patient should be contacted via phone to discuss the need for a dosing modification and should be asked to return to the investigative site as soon as possible if a new bottle of investigational product is required to be dispensed.~~		
Section 7.6, Close Observation	New Section	**If investigational product is interrupted or discontinued as described in Section 8.4, patients should be closely monitored (contacted by the site a minimum of every 2 weeks and scheduled visits every 6 weeks; if returning to the site for a scheduled visit is not feasible, use of a local lab may be permissible at the Investigator's discretion). At a minimum, the following assessments should be conducted at each study visit:** • **Physical exam and thorough review of patient reported signs and symptoms,** • **Liver biochemistry (including ALP, ALT, AST, GGT, total and conjugated bilirubin, creatinine, and**	Per FDA request.

		albumin), prothrombin time (PT)/INR, serum electrolytes, and assessment of Child Pugh (only if the patient is at the study site) and MELD scores. **In addition, a trough pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any patient who develops an AE that is indicative of or consistent with hepatic injury or decompensation.** **The following additional monitoring procedures should be performed for events of potential hepatic injury (per FDA Guidance for Industry on Drug Induced Liver Injury) or suspected hepatic decompensation based on criteria described in Section 7.4.1, Section 7.4.2, Section 7.4.3. These cases need to be discussed with the Sponsor's Medical Monitor:** • **Repeating liver biochemistry and function tests as described in Section 7.4.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic, as clinically indicated.** • **Obtaining a more detailed history of symptoms and prior or concurrent diseases.** • **Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs potentially hepatotoxic,**	

		continued use of investigational product should be discussed with the Sponsor's Medical Monitor. The patient may be discontinued from investigational product, if clinically appropriate. • **Obtaining a history of exposure to environmental chemical agents or herbal supplements which may be associated with liver toxicity.** • **Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute HBV infection), and E; autoimmune or alcoholic hepatitis; Wilson's disease, hypoxic/ischemic hepatopathy; and biliary tract disease.** • **Investigators should consider testing for Hepatitis E virus when assessing for hepatic decompensation as infection with Hepatitis E virus in patients with chronic liver diseases such as PBC may rapidly worsen with signs and symptoms similar to drug induce liver injury (Kumar 2013)** • **Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).** • **Seeking hepatology consultation, if the Investigator is not a hepatologist**	
Section 8.4, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	Investigational product may be temporarily decreased (eg, ~~by decreasing dosing frequency~~) or temporarily or permanently stopped based on tolerability concerns. ~~The dose~~ of investigational product should be ~~resumed to the maintenance dose in a blinded manner once the issues relating to the lack of~~ tolerability ~~are resolved~~. ~~Patients who are discontinued from~~ investigational product ~~prior to completion of the study are encouraged~~	Investigational product may be temporarily decreased (eg, **from 10 mg twice weekly to 5 mg twice weekly, or from 5 mg twice weekly to 5 mg once weekly**) or temporarily or permanently stopped based on tolerability concerns. **Investigational product may be resumed at the maintenance dose upon resolution** of **gastroenteritis or worsening renal function or dehydration if there is no evidence of liver injury.**	Per FDA request.

	~~to~~ continue to follow the regular visit schedule, with the exception of PK sampling, but may withdraw consent at any time.	**For rechallenge following all other dose interruptions (see Table 5),** investigational product should be **initiated at a lower dose and patients monitored more frequently with up-titration considered based on** tolerability. **Adjustments, interruptions, discontinuation, and any rechallenge of** investigational product **should be implemented per the criteria outlined in Table 5. Patients that discontinue investigational product are expected** to continue **in the study (and** follow the regular visit schedule, with the exception of PK sampling **[trough PK may be required in the event of an AE consistent with hepatic injury or decompensation]) until the end of the study**, but may withdraw consent at any time. **Table 5 Criteria for Dose Adjustment, Interruption, Discontinuation, and Rechallenge**	
8.4.1, Reasons for Additional Monitoring of Mandatory Interruption of Investigational Product; 8.4.1.1, Reasons for Additional Monitoring Related to Liver Chemistries; 8.4.1.2, Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries; 8.4.1.3, Pregnancy; 8.4.2., Reasons for Mandatory Discontinuation of Investigational Product	~~8.4.1. Reasons for Additional Monitoring or Mandatory Interruption of Investigational Product~~ ~~8.4.1.1. Reasons for Additional Monitoring Related to Liver Chemistries~~ ~~Patients who develop ALT or AST >2× baseline (and >ULN) or total bilirubin >1.5× baseline (and >ULN) should have repeat testing within 48 to 72 hours to confirm values. Patients with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or INR with persistent increases in ALT or AST should also be closely monitored.~~ ~~8.4.1.2. Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries~~ ~~Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:~~ ~~• AST and/or ALT >3× baseline (and >ULN)~~ ~~• Total bilirubin >2× baseline (and >ULN)~~ ~~Repeat testing within 48 to 72 hours to confirm the abnormalities and to determine if they are increasing or decreasing should be performed. Detailed adverse event information should also be collected, and the patient should be investigated for possible causes of the liver~~	Deletion	Replaced by text in in other sections added per FDA request.

	~~chemistry changes, as appropriate. The Investigator should obtain a history of concomitant medications (including nonprescription medications and herbal and dietary supplement preparations) and other possible causes of liver enzyme and bilirubin increases. Any potentially hepatotoxic medications should be identified and discontinued if advisable.~~ ~~If symptoms persist or repeat testing shows AST or ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), patients should be followed as clinically indicated depending on other laboratory and clinical signs and symptoms.~~ ~~For the purposes of this protocol, if the above referenced significant elevation in liver enzyme or bilirubin levels resolve following interruption of investigational product and no other cause for the elevation is identified, the elevations should be assumed to be related to investigational product and investigational product should be discontinued. If the liver enzyme or bilirubin levels do not resolve following interruption of investigational product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the patient may be re-challenged following a discussion between the Investigator or designee and the Sponsor.~~ ~~Elevation of liver enzymes or bilirubin is based on comparison to baseline values defined as the mean of all available Screening and Day 1 values, which are the mean of all available evaluations prior to the first administration of investigational product. At least 2 of these samples will be obtained a minimum of 2 weeks apart during the Screening period. Elevations that occur gradually over the course of the study may be indicative of disease progression and should be assessed as clinically appropriate. Liver enzyme and bilirubin elevations that occur over a shorter time, such as within a 6-month period, should be evaluated for drug-induced liver injury as provided in the guidelines below.~~ ~~If at any time a patient develops signs or symptoms of hepatotoxicity such as new-onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>7%) in combination with elevations in liver enzymes, investigational product~~		

	~~should be interrupted and liver enzymes monitored until signs or symptoms resolve.~~ ~~Patients who develop evidence of severe drug-induced liver injury that is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged. Severe drug-induced liver injury includes, but is not limited to, functional hepatic impairment, as indicated by rising bilirubin or INR that cannot be explained by progression of disease. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued.~~ ~~If after all investigations and actions outlined above have been completed, the investigator determines that the elevations in liver biochemistries are considered not related to investigational product, the Sponsor must be contacted before investigational product can be reinitiated. Follow-up procedures for patients resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment. Results must be reported to the site as soon as possible so the Investigator can determine if it is appropriate for the patient to continue treatment.~~ ~~The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.~~ ~~All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 15.9).~~ ~~8.4.1.3. Pregnancy~~ ~~If a female patient becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 13.1.9 pregnancy is not considered an AE for reporting purposes. The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 13.1.9). New baseline procedures should include pregnancy testing.~~		

	~~8.4.2. Reasons for Mandatory Discontinuation of Investigational Product~~ ~~Patients who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these patients should be encouraged to consent to the semiannual telephone contact and/or continued record review only to allow for secondary outcome events data to be collected.~~		
Section	**Original Text (Version 2)**	**Revised Text (Version 3)**	**Key Change** **Reasons / Justification for Change**
Section 9.5.2., Patient Numbers	~~Patients will be identified by a~~ unique ~~6-digit number,~~ independent of the randomization number. The first 3 digits ~~will~~ represent the site number and the last ~~three~~ digits ~~will~~ represent ~~the Screening~~ number.	**Patients are assigned using a** unique **10-character identifier (AAA-BBBCCC),** independent of the randomization number. The first 3 digits **represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits** represent the site number **(BBB). The** last **3** digits represent **a unique screening** number **that is assigned in sequential order at each site starting with 001 (CCC).**	Update per current practice.
Section 9.7.2, Informed Consent Procedures	The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated consent form. ~~Patients will also be provided a separate ICF before providing blood samples for genetic analysis and must be willing and able to provide consent as described above.~~	The Investigator or designee will explain the nature, purpose, possible risk, and benefit of the study to the patient and will provide him/her with a copy of the informed consent form (ICF). The patient will be given sufficient time to consider the study before deciding whether or not to participate. The patient will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The patient must be willing and able to provide written informed consent (on hard copies) before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the patient. The patient will be given a copy of the patient information sheet (PIS) and his/her signed and dated **informed** consent form **(ICF)**.	Correction. There is no separate ICF for this study.

Section 9.7.4, Screening Procedures (14 Days to 28 Days prior to Day 1)	Insertion	• Perform an ultrasound for HCC surveillance and **evaluation of gallbladder status** (if equipment is unavailable, sites should make every attempt to use available community referral sites). If…	Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications).
Section 9.7.5, Day 1 Procedures (Randomization)	• Obtain blood samples for o Serum chemistry, hematology, and coagulation o Markers of ~~inflammation and~~ fibrosis (~~IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30,~~ ELF [HA, P3NP, and TIMP 1]) o Fasting PK assessment o Bile Acid/C4/FGF-19 • Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit.	… • Obtain blood samples for o Serum chemistry, hematology, and coagulation o Markers of fibrosis (ELF [HA, P3NP, and TIMP 1]) o Fasting PK assessment o Bile Acid/C4/FGF-19 • Perform TE using the Fibroscan® TE device. If the TE cannot be performed on Day 1 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc.), the procedure may be completed within the Day 1 Visit window, (if data is needed for cirrhosis assessment) or as close as possible to the Day 1 Visit, preferably, after patient eligibility has been confirmed. Instruct the patient to take Day 1 dose on the day of this visit. • **If ultrasound for gallbladder assessment was not performed at Screening and the historic ultrasound is >12 months from Day 1, perform ultrasound.**	Markers of inflammation were removed to simplify the study design. Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications).

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 9.7.5, Day 1 Procedures (Randomization); Section 9.7.11, Week 48 Procedures; 9.7.12, Every 3 Months after Week 48	• Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s)~~; s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and~~ – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	• Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s) **to the visit** – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	Correction. Patients will only be dosed in the clinic on visits with Serial PK.
Section 9.7.6, Week 3 **and Week 42** Safety Visit Procedures	Insertions.	Week 3 **and Week 42** Safety Visit Procedures … • Assess investigational product compliance, perform investigational product accountability. • **For Week 42 Only: Assess for dose titration, if eligible. (Refer to Section 7.3)** • **For Week 42 Only: Dispense investigational product only if there is dose increase or as needed. No new investigational product bottles will be dispensed if there is only change in dosing frequency of the same dose level. Patients are expected to use up each investigational product bottle before a new bottle will be dispensed** • Obtain blood samples for - Serum chemistry, hematology, and coagulation • Schedule the next visit (Week 6 **or Week 48**), reiterate dosing instructions, and advise the patient: **For Week 3 Only:** - Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken	Correction to add Week 42 visit. Additional clarifications needed to distinguish certain assessments from Week 3. Clarification on which visits will have in-clinic dosing.

		on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3). **- NOT to take investigational product on the morning of the next visit, and** **- To bring the investigational product bottle(s) to the visit** **- To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.** **For Week 42 Only:** - NOT to take investigational product on the morning of the next visit, and - To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	
Section 9.7.7, Week 6 Procedures	Insertion	**Week 6 Visit should occur 3, 4, or 5 days after taking the Week 6 dose, eg, if the Week 6 dose is taken on a Sunday, the patient should come in for the Week 6 Visit within the following Wednesday and Friday (Figure 3).**	Clarification.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 9.7.9, Week 12, Week 24, Week 36 Procedures	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of ~~inflammation and~~ fibrosis (~~IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30,~~ ELF [HA, P3NP, and TIMP 1]) – Bile Acid/C4/FGF-19 – Fasting PK assessment … • Serial PK assessment at Week 12 and 24 ONLY (not done at Week 36~~ and Week 42~~); the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of fibrosis (ELF [HA, P3NP, and TIMP 1]) – Bile Acid/C4/FGF-19 – Fasting PK assessment (**Week 36 only**) … • Serial PK assessment at Week 12 and 24 ONLY (not done at Week 36); the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)	Markers of inflammation were removed to simplify the study design. Clarification of serial and fasting PK assessments. Clarification of water and meal restrictions on visit day. Clarification of which visits have in-clinic dosing.

	– Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose Note: Patients should only consume a meal following the 4-hour and 7-ho~~ur PK assessment times (see Figure 4). Patients should not drink any water until at least one hour postdose.~~ • Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	– Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose Note: Patients should **not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.** • Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s) **to visits**; s/he will dose at the clinic **for Week 18 and Week 30 visits** (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	
Section 9.7.10, Week 18 and Week 30 Procedures	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Bile Acid/C4/FGF-19 ~~– Fasting PK assessment~~ …	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Bile Acid/C4/FGF-19 …	Fasting PK removed; serial PK on this visit is fasted. Clarification of water and meal restrictions on visit day Clarification on which visits will have in-clinic dosing.

	• Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose ~~Note: Patients should only consume a meal following the 4-hour and 7-hour PK assessment times (see Figure 4). Patients should not drink any water until at least one hour postdose.~~ • Schedule the next visit, reiterate dosing instructions, and advise the patient: – NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s); s/he will dose at the clinic (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is	• Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the patient to swallow the tablet whole; s/he must not chew, divide, or crush the tablet. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours postdose **Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.** • Schedule the next visit, reiterate dosing instructions, and advise the patient:	

	required prior to all study visits, but water is permitted.	– NOT to take investigational product on the morning of the next visit, and – To bring the investigational product bottle(s) **to both visits**; s/he will dose at the clinic **on Week 24** (if this is in compliance with the established dosing frequency), and – To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all study visits, but water is permitted.	
9.7.11, Week 48 Procedures	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of ~~inflammation and~~ fibrosis (~~IL-6, hs-CRP, TNF-α, IgM, IgG, IgA, CK-18-M30,~~ ELF [HA, P3NP, and TIMP 1]) – ~~Fasting PK assessment~~ – Bile Acids/C4/FGF-19 • Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon	… • Obtain blood samples for – Serum chemistry, hematology, and coagulation – Markers of fibrosis (ELF [HA, P3NP, and TIMP 1]) – Bile Acids/C4/FGF-19 • Serial PK assessment; the following procedures will be conducted in all patients: – 30 minutes prior to dosing: collect predose blood sample – Dispense/Administer investigational product from the double-blind bottle (collected from the patient upon arrival for this visit) with 240 mL (8 oz.) of water. – Collect blood samples at: 30 min, 45 min, 1 hour postdose	Markers of inflammation were removed to simplify the study design. Fasting PK removed; serial PK on this visit is fasted. Clarification of water and meal restrictions on visit day

	arrival for this visit) with 240 mL (8 oz.) of water. – Collect blood samples at: 30 min, 45 min, 1 hour postdose – Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose ~~Note: Patients should only consume meal following the 4-hour and 7-hour PK assessment times (see Figure 4). Patients should not drink any water until at least one hour post dose~~	– Immediately following 1 hour post dose blood draw, administer meal replacement (to be consumed within 5 – 10 minutes) – Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post dose **Note: Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection (see Figure 4). The 24-hour post-dose sample can be obtained upon return to the clinic or by a home health care designee.**	
Section 12.1, Pharmacokinetic Blood Sampling	… Week 6 Visit should occur 3, 4, or 5 days after the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure ~~2~~]). … Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be provided following collection of the 1-, 4-, and 7-hour PK sample~~; the meal will be a meal~~	… Week 6 Visit should occur 3, 4, or 5 days after the Week 6 dose (eg, if the Week 6 dose of investigational product is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday [Figure **3**]). … **During the treatment period:** • **Pharmacokinetic fasting samples will be obtained from all patients at Day 1, and Weeks 6, 12, 18, 24, 30, 36, and 48**	Clarifications.

	~~replacement drink with nutrition~~ information ~~that has been~~ submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the ~~7~~-hour sample collection. ~~During the treatment period:~~ ~~• Pharmacokinetic fasting samples will be obtained from all patients at Weeks 6, 12, 18, 24, 30, 36, and 48 prior to dose administration in accordance with Figure 3.~~ ~~• Serial PK assessments will be performed in all patients at Weeks 12, 18, 24, 30, and 48.~~	**prior to dose administration in accordance with Figure 4.** • **Serial PK assessments will be performe in all patients at Weeks 12, 18, 24, 30, and 48.** Patients should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal **replacement drink** will be provided following collection of the 1-, 4-, and 7-hour PK sample. **The nutritional** information **of the meal replacement drink should be** submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the **9-**hour sample collection.	
Section 13.1.1.1, Adverse Event	Insertion	**Patients should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as: pale-colored stools, urine color from pale to deep amber [dark], nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or the whites of eyes, and bruising easily.**	Given this is an at risk population, patients should be reminded to contact the Investigator or study coordinator in case they experience side effects or any other medical concerns and be aware of the signs and symptoms of potential hepatic decompensation.
Section 13.1.1.4, Adverse Events of Special Interest	Insertion	**The following decompensation events are adverse events of special interest; a subset of these are also captured as additional efficacy assessments (see Section 14.2.3).** • **Variceal bleeding or recurrent variceal bleeding documented by endoscopy OR patient presenting with anemia or melena (hemoglobin drop ≥2 gm/dL) and found to have varices documented by endoscopy,**	Per FDA request.

		irrespective of hospitalization or requirement of blood transfusion. • **Gastrointestinal bleeding as a result of gastric or duodenal varices verified by endoscopy** • **Hepatic encephalopathy, Grade ≥2** • **New onset ascites requiring treatment** • **Worsening of ascites (requiring increase in drug therapy or requirement of surgical procedure such as paracentesis or shunt placement)** • **Refractory ascites -unresponsive to medications, and patient is not a candidate for TIPS or shunt and requires large volume paracentesis** • **Hyponatremia (Na ≤125 mEq/L) secondary to ascites** • **Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis-by cell count/chemistry)** • **Hepatorenal syndrome Type 1 and Type 2 and Acute Kidney Injury (AKI)** • **Liver failure defined as worsening of liver synthetic function that is persistently worse relative to baseline and/or progressive over time:** – **Hepato-pulmonary syndrome** – **Porto-pulmonary syndrome** – **Liver Transplant** – **Increase in MELD scores by 3 points relative to baseline, persistent over time and unrelated to vitamin K deficiency related increase in INR**	

		– **Any liver related event that requires hospitalization and treatment**	
Section 13.1.4.1, Reporting of Adverse Events	Insertion	**In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any patient.**	Enhanced communication of the Investigator and Medical Monitor in the event of signs or symptoms of hepatic decompensation.
Section 13.1.8, Follow-Up of Adverse Events and Serious Adverse Events	AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. ~~If resolved, a resolution date for the AE should be documented on the eCRF.~~ The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator. All patients showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.	AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. The Investigator must ensure that follow up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator. **Drug-Induced Liver Injury or Disease Progression** All patients showing possible drug-induced liver injury **or disease progression** should be followed until all abnormalities return to normal or to the baseline state. Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the eCRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease. **Cholecystitis or Pancreatitis** **Patients should be instructed to contact the investigational site if they experience any of the following signs and symptoms: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, or weakness. Patients should also be counseled to seek immediate medical assistance if they experience persistent severe abdominal pain.** **In the event that cholecystitis and/or pancreatitis is suspected, Investigators should promptly bring patients into the clinic to undergo a complete**	Increased monitoring per standard of care if a patient is diagnosed or develops symptoms consistent with pancreatitis.

		evaluation, including a physical examination, and laboratory assessments [ie, amylase and lipase]). Investigators should refer to standard of care guidelines on suspected pancreatitis (Banks 2012, Greenburg 2015). Diagnosis of acute pancreatitis includes 2 of the following: **• Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)** **• Serum lipase activity (or amylase) at least 3 times greater than the upper limit of normal** **• Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging** **To ensure appropriate vigilance, amylase and lipase levels should be monitored monthly for 3 months after onset of symptoms, irrespective of whether a diagnosis of cholecystitis and or pancreatitis is confirmed. The Investigator should contact the Medical Monitor upon awareness of the above (ie, suspected or confirmed diagnosis).** Results should be recorded promptly in the eCRF.	
Section 13.1.9, Pregnancy and Follow-Up	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must ~~interrupt~~ treatment with investigational product immediately (see Section 8.4.1.3) and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD. The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor. ~~The patient may restart investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The patient must have a negative pregnancy test before restarting investigational product. If a patient's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy confirmed by a serum β-hCG test before restarting investigational product.~~	Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must **discontinue** treatment with investigational product immediately and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to PPD or faxed to PPD. The patient and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.	Per new study-specific safety updates, pregnancy will require discontinuation and no option to restart.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 13.2.2., Medical and Surgical Procedures	New Section	**Medical and surgical procedures will be recorded at the visits indicated in Table 1.**	Section added for consistently with Schedule of Events.
Section 13.2.5, Electrocardiogram	Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time. ~~Full instructions will be provided for forwarding the ECGs for central reading.~~	Investigative sites must retain a copy of all ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Patient ID number, date, and time.	Correction.

Section 13.2.6, Laboratory Assessments

Table ~~9~~ List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen, creatinine~~, direct bilirubin, total bilirubin,~~ aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, TFT (TSH, free T3 and free T4)
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)
Coagulation	PT, PTT, INR
Urinalysis (dipstick)	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, ~~albumin, creatine,~~ leucocytes, nitrates, albumin/~~creatine~~ ratio (if positive~~), pregnancy~~
~~Markers of Inflammation~~	~~IL-6, hs-CRP, TNF-α, IgM, IgA, IgG, CK-18-M30~~
Noninvasive measurements of liver fibrosis~~, liver stiffness and cirrhosis~~	ELF (HA, P3NP, and TIMP-1) ~~TE~~
PK assessments	OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)

Table **11** List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen, creatinine, direct bilirubin, total bilirubin, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, **total bilirubin,** free fatty acids, TFT (TSH, free T3 and free T4)
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC)
Coagulation	PT, PTT, INR
Urinalysis (dipstick)	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, leucocytes, nitrates**; albumin, creatinine**, albumin/**creatinine** ratio (if positive**); β-hCG**
Markers of Cholecystitis and Pancreatitis	**Amylase and lipase**

Markers of inflammation samples were removed to simplify the study design.

Amylase and lipase added per FDA request.

Total OCA calculation update is a correction.

<table>
<tr><th>Section</th><th>Original Text (Version 2)</th><th>Revised Text (Version 3)</th><th>Key Change
Reasons /
Justification for Change</th></tr>
<tr><td></td><td>
<table>
<tr><td>PD markers</td><td>C4, FGF-19 and plasma bile acids</td></tr>
</table>
…
INR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, ~~Na,~~ and INR values, with modification by United Network for Organ Sharing. ~~Total OCA will be calculated based on OCA, tauro-OCA, glyco OCA, and metabolite OCA glucuronide concentrations.~~ Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.</td><td>
<table>
<tr><td>Noninvasive measurements of liver fibrosis</td><td>ELF (HA, P3NP, and TIMP-1)</td></tr>
<tr><td>PK assessments</td><td>OCA (parent and conjugates [glyco and tauro], metabolite OCA-glucuronide)</td></tr>
<tr><td>PD markers</td><td>C4, FGF-19 and plasma bile acids</td></tr>
</table>
…
NR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, and INR values, with modification by United Network for Organ Sharing. Total OCA will be calculated based on the sum of OCA, glyco-OCA, and tauro-OCA concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.</td><td></td></tr>
<tr><td>Section 14.1.1, Child-Pugh Score</td><td>Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory. ~~Investigators will be responsible for determining the appropriate dosing regimen based on the CP score (and). Any change in CP Score will necessitate re evaluation of the dosing regimen.~~</td><td>Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 12 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory.</td><td>Per new dosing guidelines, CP score will not determine dosing regimen.</td></tr>
</table>

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 14.1.2, Model of End Stage Liver Disease Score	An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival ~~and is calculated according to the following formula~~ (Kamath 2007): ~~MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43~~ ~~MELD score will be calculated and reported in whole numbers according to the frequency listed in Table 1.~~	An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival (Kamath 2007). **MELD score will be calculated and reported for visits where these parameters are measured (see Table 1).**	Text clarified since calculation is not performed by the site.
Section 14.2.1, Markers of Inflammation, Apoptosis and Necrosis	~~Markers of Inflammation, Apoptosis and Necrosis~~ ~~Blood samples for analytes including IL-6, hs-CRP, IgA, IgG, IgM, TNF-α, cytokeratin-18 neoepitope M30.~~ ~~Assessments will be performed according to the schedules presented in .~~	Deletion	Markers of inflammation were removed to simplify the study design.
Section 15.3, Pharmacokinetic Analyses	PK analysis will based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics.	PK analysis will **be** based on the PK population. Values will be calculated using non-compartmental methods. The values will be summarized by active treatment group using descriptive statistics. **Full details regarding the planned analyses, methods, and outputs for the study will be detailed in the SAP.**	Clarification.
Section 15.4, Safety Analyses	Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. ~~CP scores will be summarized by treatment group at Baseline and at each post-Baseline visit.~~ No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.	Laboratory parameters, physical examinations including vital signs, and ECGs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The absolute change from baseline will also be summarized. No inferential comparison with formal statistical hypothesis testing will be performed for safety endpoints.	Correction.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 15.4.1, Adverse Events	Insertion	**Adverse events of special interest as defined in Section 13.1.1.4 will be summarized for each treatment group.**	Per FDA request.
Section 15.4.2, Clinical Laboratory Evaluations	Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment. In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation. ~~Vital Signs and Weight~~ ~~The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.~~ ~~Electrocardiograms~~ ~~Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.~~	Laboratory parameters will be summarized in standard international (SI) system of units by treatment group using descriptive statistics at Baseline and at each on-study evaluation. Re-test or unscheduled results will not be summarized but will be included in the data listings. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment. In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at post Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post-Baseline visit will be provided for hematology and serum chemistry by treatment group to assess changes in laboratory values from Baseline to each on-study evaluation.	Correction. Moved to separate section since not laboratory evaluations.

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 15.4.3, Additional Safety Analysis	New Section	**<u>Vital Signs and Weight</u>** **The results and change from Baseline to each on-study evaluation visit will be summarized by treatment group for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.** **<u>Electrocardiograms</u>** **Electrocardiogram (ECG) results will be summarized at each on-study visit descriptively, including the number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant results at Baseline and each on-study evaluation.**	Separate section created per above deletion.
Section 15.5, Efficacy Analyses	Risk Scores: Changes from baseline in the MELD score and in CP score will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.	Risk Scores: Changes from baseline in the MELD score and in CP score**, C4, FGF-19 and plasma bile acids** will be summarized and analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.	Clarification.
Section 15.6, Additional Efficacy Analyses	Analyses of changes in liver stiffness and ELF~~, cytokeratin~~ and TIMP-1~~, and markers of inflammation~~ will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin. …	Analyses of changes in liver stiffness **(TE)** and **liver fibrosis (**ELF **[HA, P3NP,** and TIMP-1**])** will be summarized and analyzed using the same methodology specified for the key secondary analyses of change in bilirubin. … **Full details regarding additional efficacy analyses will be detailed in the SAP.**	Clarification

Section	Original Text (Version 2)	Revised Text (Version 3)	Key Change Reasons / Justification for Change
Section 21, List of references	Insertion	**Banks O, Bollen T, Dervenis C, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013; 62:102-111.** **…** **Greenburg J., Hsu J., Bawazeer M., et al. Clinical Practice Guideline: Management of acute pancreatitis. Can J Surg. 2016; 59 (2):128-140.** **…** **Kumar A, Saraswat VA. Hepatitis E and Acute-on-Chronic Liver Failure. Journal of clinical and experimental hepatology. 2013 Sep;3(3):225-30.** **…** **Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014 Aug;60(2):715-35.**	New references added per added cited content.

APPENDIX C. SUMMARY OF CHANGES: PROTOCOL 747-401 VERSION 4 (DATED 15 FEB 2019)

Protocol 747-401 was revised to include the following information:

- Updated clinical development data based on IB Version 18 (31 January 2019).
- Exclusion criteria were updated to mitigate the inclusion of subjects who may be pregnant or breastfeeding as an additional safety precaution or who have a known history of human immunodeficiency syndrome infection.
- Exclusion criteria and prohibited medications sections were updated to prevent the concomitant use of fibrates and OCA. The primary objective of this study is to characterize the pharmacokinetics of OCA in patients with PBC and mild to severe hepatic impairment. The drug-drug interactions of OCA with fibrates have not yet been fully characterized in any population and are being restricted in this study as an additional safety precaution until data are available in a less advanced population.

Summary of Changes

The following revisions were made to the protocol in Protocol Version 4. Revised and new text in Version 4 is indicated in bold font, and the text deleted from Protocol Version 3 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below.

Section	Original Text (Version 3)	Revised Text (Version 4)	Key Change Reasons / Justification for Change
Title Page	Version 3: 04 Jan 2018	Version **4: 15 Feb 2019** ~~3: 04 Jan 2018~~	Date of Update
Study Personnel Contact Information	PPD MD Senior Medical Director, Clinical Division INC Research/inVentiv Health PPD PPD	PPD MD Senior Medical Director, Clinical Division ~~INC Research/inVentiv Health~~ **Syneos Health** PPD PPD ~~om~~ **Ray.**	Personnel Information Update
Synopsis	The study is planned to have approximately 35 investigational sites, globally.	The study is planned to have approximately ~~35~~ **50** investigational sites, globally.	Number of sites expanded to improve study recruitment as the patients in this study represent a small subset of an orphan disease.
5.1	Study 747-401 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC (ie, in the US, Canada, and the EU). In all other regions, this study is considered Phase 3b.	**Since then, other countries have received approval (eg, Australia and Switzerland).** Study 747-401 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC ~~(ie, in the US, Canada, and the EU). In~~; in all other regions, this study is considered Phase 3b.	
5.3	As of 13 Oct 2017, approximately 2690 subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 552 patients had PBC, 1141 patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, 73 patients had primary sclerosing cholangitis (PSC), and 6 patients had biliary atresia.	**As of 28 October 2018, approximately 3470 subjects have received ≥ 1 dose of OCA. This estimation includes subjects from blinded ongoing studies. Of these 3470 subjects, 888 were healthy volunteers, 580 subjects had PBC, 72 subjects had PSC, 6 subjects had biliary atresia, 41 subjects had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 1914 subjects had NASH, and 33 subjects had portal hypertension due to alcoholic cirrhosis.** ~~As of 13 Oct 2017, approximately 2690 subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 552 patients had PBC, 1141 patients had nonalcoholic steatohepatitis (NASH), 41 patients had diabetes mellitus/ nonalcoholic fatty liver disease (NAFLD), 33 patients had alcoholic cirrhosis/portal hypertension, 73 patients had primary~~	Updated per latest Investigational Brochure

		~~sclerosing cholangitis (PSC), and 6 patients had biliary atresia.~~	
5.6	Recent safety findings in NASH clinical trials include 2 cases of hepatic decompensation reported as SUSARs, 1 of which resulted in death. Both cases involved numerous confounding factors that make evaluation of association with treatment difficult. Details for both events are provided in the Investigator's Brochure Addendum 1 to Version Number: 16 (31 March 2017), Effective Date: 02 October 2017. The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease. Changes in lipid profiles have also been observed with OCA dosing, including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further. Independent data monitoring committees (DMCs) have performed detailed reviews of several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification. <u>Post-Marketing Cases in PBC</u>	**Ongoing NASH clinical trials include reports of hepatic decompensation assessed as suspected unexpected serious adverse reactions (SUSARs). Data remain blinded. Additional details of these SUSARs are provided in the IB Version Number: 18 (31 January 2019).** ~~Recent safety findings in NASH clinical trials include 2 cases of hepatic decompensation reported as SUSARs, 1 of which resulted in death. Both cases involved numerous confounding factors that make evaluation of association with treatment difficult. Details for both events are provided in the Investigator's Brochure Addendum 1 to Version Number: 16 (31 March 2017), Effective Date: 02 October 2017.~~ The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease. Changes in lipid profiles have also been observed with OCA dosing, including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further. **An independent data monitoring committee (DMC) has performed detailed reviews of ongoing studies of obeticholic acid, including the Phase 3/4, clinical outcomes study in PBC (747-302), this Phase 4 PK and safety study in patients with PBC (747-401), the**	Updated per latest Investigational Brochure

	As of September 2017, greater than 3000 patients have received Ocaliva® in the post-marketing setting. In patients with moderate to severe hepatic impairment (Child-Pugh B and C), liver decompensation, liver failure, and death have been reported when Ocaliva was dosed up to 7 times the recommended once weekly starting dose for such patients.	**Phase 3, pivotal study in NASH with fibrosis (747-303), and the Phase 3 study in NASH with cirrhosis (747 304). The DMC will continue to review data quarterly and will provide oversight of the above-mentioned studies throughout the course of the development program. Additional details are provided in IB Version Number: 18 (31 January 2019).** ~~Independent data monitoring committees (DMCs) have performed detailed reviews of several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification.~~ <u>Post-Marketing Cases in PBC</u> As of ~~September~~ ~~2017~~ **October 2018**, greater than ~~3000~~ **4200** patients have received Ocaliva® in the post-marketing setting. In patients with moderate to severe hepatic impairment (Child-Pugh B and C), liver decompensation, liver failure, and death have been reported when Ocaliva was dosed up to 7 times the recommended once weekly starting dose for such patients.	
8.1	This study will be conducted at approximately 35 international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B and CP-C.	This study will be conducted at approximately ~~35~~ **50** international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B and CP-C.	Number of sites expanded to improve study recruitment as the patients in this study represent a small subset of an orphan disease.

8.3	Addition	**14. Known history of human immunodeficiency virus infection** **15. Treatment with commercially available fibrates or participation in a previous study involving fibrates within 3 months before Screening, or plans to use commercially available fibrates during the study** **16. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating**	Addition made to exclusion criteria as a safety precaution
9.2.2	Addition	**Fibric acid derivatives (ie, fibrates such as fenofibrate and bezafibrate) are also prohibited while on investigational product.**	Addition made to prohibited medication as a safety precaution

Clinical Study Protocol 747-401

OBETICHOLIC ACID (OCA)

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

Addendum 1: 19 May 2020

Country-Specific Protocol Addendum for Multiple Countries

EudraCT Number: 2017-001762-13

Sponsor

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CONFIDENTIAL

SPONSOR'S APPROVAL OF THE PROTOCOL ADDENDUM

Reviewed and Approved by:

PPD

PPD

PPD , MD MAS

26 MAY 2020

Date

Executive Vice President, Research and Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA), Protocol 747-401, and this addendum. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected subjects according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-401 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____

Investigator's Name (Printed)

_____ _____

Investigator's Signature Date

COUNTRY-SPECIFIC ADDENDUM TO PROTOCOL 747-401 FOR MULTIPLE COUNTRIES

1. OVERVIEW AND RATIONALE

The restrictions that have recently been imposed to contain the global COVID-19 pandemic, such as social distancing measures, stay at home orders, and other limitations have impeded the ability of subjects and site staff to complete protocol-specified procedures. Some study sites are not able to perform protocol-specified procedures and assessments. In addition, some subjects are unable to return to study sites for evaluations and/or to receive continued supply of investigational product (IP). The purpose of this Country-Specific Protocol Addendum is to describe the requirements and processes under which subjects who are unable to return to study sites may complete protocol specified assessments and continue to receive investigational product until in-person site visits can resume. In an effort to minimize the potential adverse impact of restrictions from the COVID-19 pandemic on achieving the objectives of the study, while continuing to ensure the safety of participating subjects, the following approaches will apply to the study protocol, effective immediately.

1.1. Alternative Approaches for Subject Assessments and Procedures and Continuation of Treatment with Investigational Product During COVID-19 Pandemic

Assessment of subject status must occur prior to the release of additional investigational product. For subjects who are unable to attend in-person study visits due to COVID-19 restrictions, the following alternative options are deemed acceptable to satisfy the requirements for continued supply of investigational product.

All assessments should adhere as close as possible to the visit windows specified in the protocol schedule of visits. Implementation of alternative means of assessing subjects as well as changes in visit windows to assess subjects must be documented by the Investigator. Subjects who are temporarily unable to attend scheduled visits should be encouraged to return to the study site as soon as practically feasible for completion of protocol-specified assessments and procedures that could not be performed due to restrictions or limitations during the COVID-19 pandemic.

1.1.1. Telemedicine Visits

In place of in-person visits, assessment of subjects may be performed using a telemedicine "virtual visit" as an alternative means of enabling Investigators and site staff to interact with study subjects. The provision of telemedicine software is cloud-based and available across platforms, compliant with HIPPA/GDPR and 21 CFR Part 11, and intuitive to use. It allows the Investigator and staff to efficiently contact and engage subjects remotely from any location.

The established telemedicine procedures will be defined at the institution, and at a minimum, must consist of a direct telephone or video call discussion with the subject by the Investigator or by an appropriate designee from the study team who is currently authorized to undertake examinations on the study per Delegation of Authority Log. Assessment of subjects in this manner is to be documented by the Investigator.

If an onsite visit or a telemedicine contact is not feasible (eg, no access to the subject) to assess subject status, investigational product is not to be released.

1.1.2. Laboratory Tests

In addition to telemedicine visits, assessment of safety laboratory tests (chemistry panel including glucose, hematology panel, coagulation parameters, computed MELD score, and CP score), a lipid panel, and liver laboratory tests (eg, ALT, AST, bilirubin), will need to be performed at appropriate study visits as specified in the protocol. If laboratory tests cannot be obtained at the study site due to COVID-19 restrictions, they may be performed and analyzed at a local laboratory. The results of all laboratory tests and the reference ranges for each laboratory test are to be sent to the Investigator. The results of the laboratory tests will be reviewed by the Investigator and with the Medical Monitor, if necessary.

1.1.3. Home Health Care Visits

If laboratory tests cannot be obtained from local laboratories, home nursing support is an accepted option that may be employed to supplement telemedicine interactions to enable the collection and processing of blood samples for laboratory tests, and conduct other limited assessments (eg, assessment of vital signs). The home healthcare visits will be performed by qualified health care providers including registered and licensed nurses or physicians.

1.1.4. Virtual Study Hub

To enable continued support of subjects who are enrolled at sites that may not be able to evaluate subjects during the COVID-19 pandemic, study sites may temporarily transfer responsibility for their subjects to a dedicated study site acting as a virtual study hub to provide support and oversight of such subjects. In this instance, qualified Investigators who are participating in Intercept's PBC studies and are at the dedicated study sites will assume the responsibilities for the medical care of the subjects through telemedicine and home-nurse support according to the assessments and procedures described in the protocol. Subjects will be transferred to sites that are approved for the specific PBC study that the subject is participating in. The transfer of subjects and all assessments and procedures will be documented.

1.2. Investigational Product

Based on the individual subject level safety and tolerability assessments, if the Investigator considers that the benefit-risk profile remains favorable, investigational product may be dispensed to subjects, according to protocol. Investigational product may be sent directly to the subject from either the study site or a study drug depot via a courier service if subjects are not able to attend study site visits. Direct shipment of investigational product from the Investigator sites to subjects is to adhere to the site's institutional and pharmacy procedures. Approval for each shipment of investigational product is to be obtained and documented by the Investigator.

Unless the Investigator is able to evaluate safety and tolerability and assess the benefit-risk for the individual subject, investigational product is not to be provided.