Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

EudraCT Number: 2014-005012-42

ClinicalTrials.gov Identifier: NCT02308111

Sponsor

Intercept Pharmaceuticals, Inc.
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Morristown, NJ 07960
USA

16.1.1 PROTOCOL AND AMENDMENTS

Protocol 747-302, Version 1, dated 03 Oct 2014

Protocol 747-302, Amendment 1, dated 29 Apr 2015

Protocol 747-302, Amendment 1.1, dated 12 Nov 2015

Protocol 747-302, Version 3, dated 07 Sept 2016

Protocol 747-302, Version 3.1 (FDA Review Only), dated 21 Dec 2016

Protocol 747- 302, Version 4, dated 10 May 2017

Protocol 747- 302, Version 5, dated 04 Jan 2018

Protocol 747- 302, Version 6, dated 05 Nov 2019

Protocol Addendums

Addendum 1 Netherlands to Protocol 747- 302, dated 18 Jan 2017

Addendum 2 to Protocol 747- 302, dated 27 Apr 2017

Addendum 1, Country Specific (Turkey) to Protocol 747- 302, dated 02 Jan 2018

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Original: 03 October 2014

Sponsor

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

06 Oct 2014

PPD PhD Date

PPD Clinical Development

Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigational Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-302. 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 (CRFs) 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

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2. SYNOPSIS

Name of Sponsor/Company: Intercept Pharmaceuticals, Inc.

Name of Investigational Product: Obeticholic Acid (OCA)

Name of Active Ingredient: OCA; 6α-ethyl chenodeoxycholic acid (6-ECDCA); INT-747

Title of Study: A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Study Number: 747-302

Study Center(s): Approximately 170 investigational study sites, globally

Study Period (Years): The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

Number of Subjects (planned): Approximately 350 subjects

Phase of Study: Phase 3b

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cirrhosis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the pharmacokinetics of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

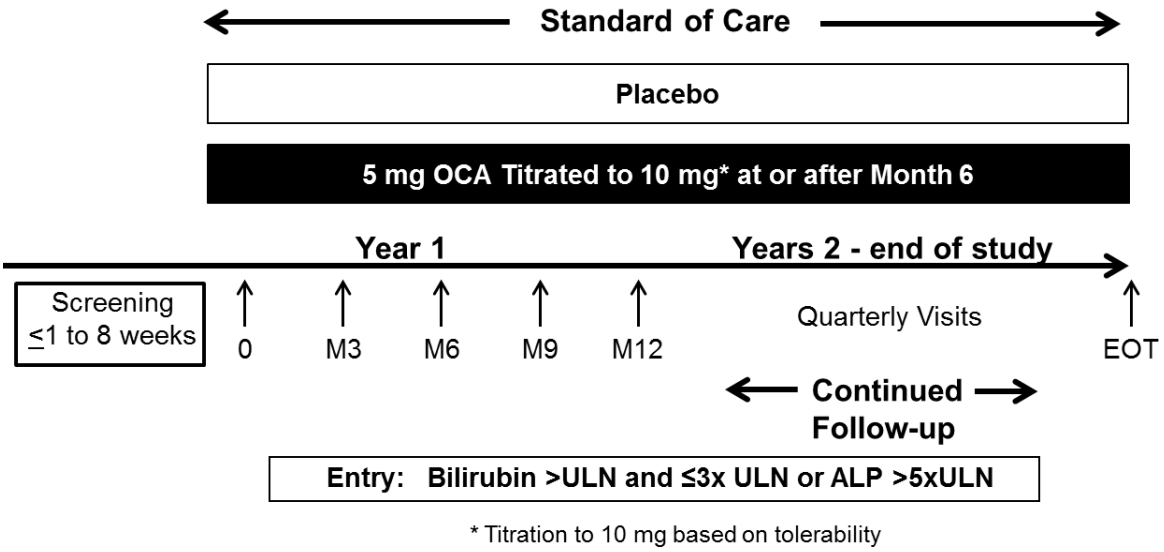
To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).

Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After 6 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 6-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.

Schematic Diagram:



EOT = end of treatment; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN
3. Age ≥18 years
4. Either is not taking UDCA (UDCA naïve or no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with an approved, stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective (≤1% failure rate) method of contraception during the study and for 30 days after the end of treatment visit
6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     - Variceal bleed
     - Uncontrolled ascites
     - Encephalopathy
     - Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or screening serum creatinine >2 mg/dL (178 μmol/L)
3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection

8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Placebo (matching tablets)

Duration of Treatment:

It is estimated that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 121 total primary endpoint events.

Duration of Subject Participation:

It is estimated that subject participation will be a minimum of approximately 6 years.

Criteria for Evaluation:

Primary Objectives	Assessments
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Change in baseline liver biochemistry	Liver biochemistry (see Table 4 for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhance liver fibrosis (ELF), and Fibroscan®
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
Pharmacokinetics	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life
Safety and tolerability	Including the following: Treatment-emergent adverse events Clinical laboratory values

Statistical Methods:

Sample Size Justification

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up
- 5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Randomized, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Every event for enrolled subjects will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory.

Other Efficacy Analyses

The following secondary efficacy analyses will compare OCA to placebo on time to the following events:

- Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above)
- Liver-related death
- Liver-related death or liver transplant
- Liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Further details on efficacy, health outcomes, and pharmacokinetic analyses are specified in Section 13.

Safety Analysis

Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will compare OCA and placebo using the Safety Population.

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

LIST OF TABLES

LIST OF FIGURES

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 gonadotrophin
BAS	bile acid sequestrants
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DEXA	dual-emission X-ray absorptiometry
DSMC	Data Safety Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhance liver fibrosis
EOT	end of treatment
FDA	Food and Drug Administration
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
HDL	high density lipoprotein
IB	Investigational Brochure

Abbreviation or Specialist Term	Explanation
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
LDL	low density lipoprotein
LTSE	Long-term safety extension
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cirrhosis
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
the Sponsor	Intercept Pharmaceuticals, Inc.
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
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 Primary Biliary Cirrhosis and Obeticholic Acid

Primary Biliary Cirrhosis (PBC) 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, is currently the only treatment approved for PBC (Lindor 2009). While UDCA therapy has a marked effect on the treatment of PBC, up to 50% of patients show a suboptimal response or no response to UDCA. Such patients are at significantly increased risk of a poor clinical outcome due to PBC disease progression. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]). Obeticholic acid (OCA) is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary human bile acid chenodeoxycholic acid (CDCA). OCA is currently being developed in the United States (US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (27 Jul 2010) for the treatment of PBC.

5.2. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC. 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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects 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 10 mg OCA 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 up to 4 years. The LSTE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rational for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. Starting subjects on 5 mg OCA and titrating to 10 mg based on the clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Doses

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.

Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.

5.5.2.2. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.

5.6. Summary of Known Potential Risks with OCA

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, but with a much lower frequency than that observed in subjects with PBC.

Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were

observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.

Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). The clinical significance of these lipid findings remains unclear and is being studied further. Notably, despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

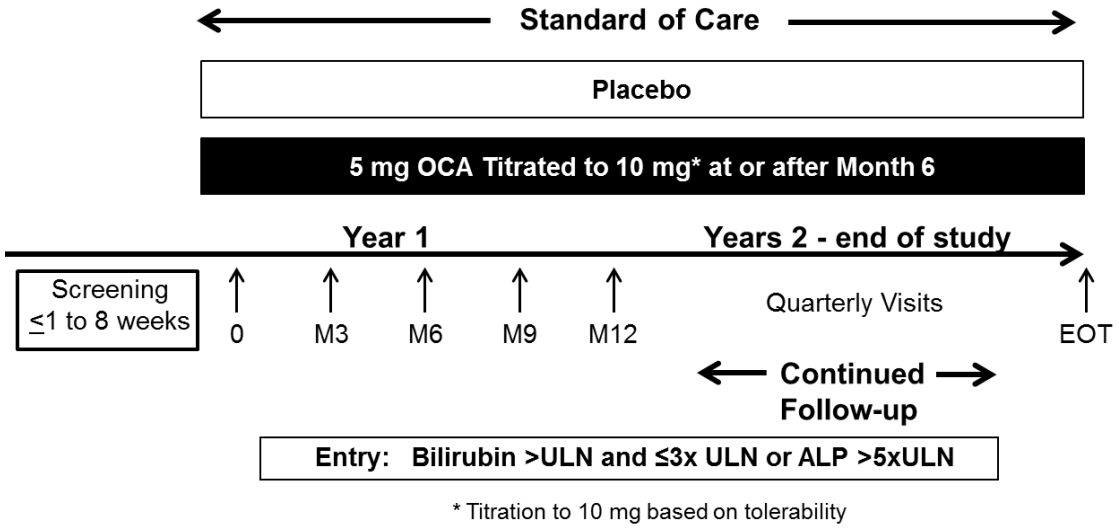
This is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤3x ULN or ALP >5x. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 350 subjects meeting all enrollment criteria will be recruited into the study over an approximate 2-year period, randomly allocated to treatment with either OCA or matching placebo once daily in a 1:1 ratio. Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). Investigational product will be taken orally, once daily. The randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used. Following 6 months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability. It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 121 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Safety Monitoring Committee; DSMC) terminates the study.

This study will be conducted at up to approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOT = end of treatment; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

	Year 1							Years 2-End of Study				
	Screening Visit x 2[a]	**Day 0**	**Safety Contact**[b]	**M 3**	**M 6**	**M 9**	**M 12**	**M 3 continued follow-up**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ ET**[c]
Visit Windows (+/-)[d]	**≤1 to 8 wks prior to Day 0**		**±1 wk**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**
STUDY PROCEDURES												
Informed Consent	X											
Medical/PBC History[e]	X											
Inclusion/Exclusion Criteria	X	X										
Physical Exam	X						X				X	X
Vital Signs (including weight)	X[f]	X		X	X	X	X[f]		X		X[f]	X[f]
12-Lead Electrocardiogram	X											X
Subject Questionnaires[g]		X			X		X		X		X	X
TE Fibroscan®/DEXA[h]		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
Randomization/Treatment Assigned		X										
Dose Titration (if applicable)[i]					X							
Dispense Investigational Product[j]		X		X	X	X	X	X	X	X	X	
IP Accountability/Compliance			X	X	X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS[k]												
Urinalysis	X	X					X				X	X
Urine-based β-hCG Pregnancy Test[l]	X	X										
Chemistry/Hematology/Coagulation	X	X		X	X	X	X	X	X	X	X	X

	Year 1							Years 2-End of Study				
	Screening Visit x 2[a]	**Day 0**	**Safety Contact**[b]	**M 3**	**M 6**	**M 9**	**M 12**	**M 3 continued follow-up**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ ET**[c]
OCA, C4, and FGF-19 (plasma)		X			X	X[m]	X				X	X
Markers of Hepatic Fibrosis and/or Inflammation[n]		X			X		X		X		X	X
Genetics[o]		X					X				X	
Blood Sample for Future Analysis[p]		X			X		X		X		X	X

β-hCG = beta human chorionic gonadotrophin; DEXA = dual-emission X-ray absorptiometry; EOT = End of Treatment; ET = Early Termination; FGF = fibroblast growth factor-19; IP = Investigational Product; M = month, wk = week

[a] All subjects will have two 2 bilirubin assessments at least 2 weeks apart including those subjects who qualify based on ALP criteria. For subjects that do not qualify based on ALP (ALP >5x ULN), the mean of the two 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN).

[b] The subject should be contacted by telephone on a monthly basis (±1 week) between at-clinic study visits, at Month 1 and Month 2, and also 2 weeks postdose titration, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.

[c] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[d] Visits should be based on Day 0 (not on the prior visit).

[e] Medical history at Screening will include smoking and alcohol consumption history and current habits for both.

[f] Height will be collected at this visit.

[g] Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale, and Quality of Life questionnaires. (See Section 11.1.2.2 and Section 12.2.5.1)

[h] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. If a TE was performed within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.

[i] After 6 months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month 6 visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.

[j] Subject to begin dosing on Day 1

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

[l] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at the site. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).

[m] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.9 for the PK sampling schedule.

[n] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[o] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.

[p] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 350 subjects will be randomized in the study to achieve 121 adjudicated primary endpoint events.

7.3. Treatment Assignment

Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 6 month study visit or at any study visit thereafter depending on tolerability.

7.4. Dose Titration Criteria

After 6 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the 6-month visit or any study visit following the 6-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.

7.4.1. Safety Criteria for Adjustment or Stopping Doses

Investigational product may be temporarily decreased (ie, from 10 mg to 5 mg daily, or by alternate day dosing) 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 (5 mg or 10 mg) once the issues relating to the lack of tolerability are resolved.

Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, her or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent.

7.5. Criteria for Study Termination

The Sponsor 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 DSMC, it may be necessary to stop the study before all subjects have completed the study. In addition, the Sponsor may terminate the study at an investigational site at any time

(eg, poorly performing sites, as determined by the number of subjects 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 subjects for the Study/Early Termination Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 121 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN
3. Age ≥18 years
4. Either is not taking UDCA (UDCA naïve or no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with an approved, stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective (≤1% failure rate) method of contraception during the study and for 30 days after the end of treatment visit
6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     - Variceal bleed
     - Uncontrolled ascites
     - Encephalopathy
     - Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening serum creatinine >2 mg/dL (178 μmol/L)
3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection

8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components

8.4. Subject Withdrawal from Investigational Product or Study Criteria

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

If a female subject becomes pregnant, she must discontinue taking investigational product, but should continue with the study visit schedule. The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes pregnancy is not considered an AE. The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotrophin (β-hCG) test.

8.4.2. Other Reasons for Discontinuation of Investigational Product

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent.

The following events are considered potential appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination and the study will only terminate at the time when the needed number of adjudicated events has accrued (or at the discretion of the Sponsor):

- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject

- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important
- Withdrawal of consent

The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.

8.4.2.1. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.2.2. Lost to Follow-up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.3. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the end of treatment (EOT) evaluations should be performed at the time of withdrawal.

9. TREATMENT OF SUBJECTS

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: placebo and OCA. Investigational product will be administered orally, once daily for the duration of the study. Each dose will be made up of 1 tablet (ie, one 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, once daily. Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time each day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

9.1.1. Dose Adjustment Beginning at Month 6

After 6 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 6 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 Day 0) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Subjects taking bile acid sequestrants (BAS) 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).

PBC Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.

9.3. Treatment Compliance

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

Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should

perform investigational product accountability and, if applicable, follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2, below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.5. Assignment of Site and Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 3 digits will represent the Screening number.

9.6. Restrictions

No additional restrictions.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0. The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Months 3-12	±2 week (7 days)
Quarterly visits (Months 15 – EOT)	±2 weeks (14 days)
EOT	As soon as possible upon study discontinuation and as near as possible to last dose taken

EOT = end of treatment

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

9.7.3. Screening Procedures (≤1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. Subjects should be reconsented, as appropriate, at this time.

Two Screening visits will occur from ≤1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values):

- All subjects will have 2 bilirubin assessments at least 2 weeks apart including those subjects who qualify based on ALP criteria.
- For subjects that do not qualify based on ALP alone (ALP >5x ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN).

Screening Visit procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Perform a standard 12-lead electrocardiogram (ECG)
- Assess and record any pretreatment-emergent AEs
- Record prior (if within 30 days of Day 0) and current concomitant medications
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.
- In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate.

9.7.4. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility
- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Subject questionnaires (see Section 12.2.5.1)
- Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device. If TE has been done within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required

- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
- Assess and record any pretreatment-emergent AEs
- Record prior (within 30 days of Day 0) and current concomitant medications
- Randomize the subject only if s/he meets all inclusion criteria and no exclusion criteria
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits
- 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 tests
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhance liver fibrosis [ELF])
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Access the IWRS and dispense investigational product
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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

9.7.5. Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone]):

- Assess and record AEs
- Review and record concomitant medications

- Assess investigational product compliance
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 3 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Assess and record AEs
- Review and record concomitant medications
- Assess investigational product compliance and perform investigational product accountability
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Schedule the next visit and assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 6 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Subject questionnaires (see Section 12.2.5.1)
- Assess and record AEs
- Review and record concomitant medications

- Assess investigational product compliance and perform investigational product accountability
- Assess for dose titration, if eligible (refer to Section 7.4)
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.8. Month 9 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Assess and record AEs
- Review and record concomitant medications
- Assess investigational product compliance and perform investigational product accountability
- Assess for dose titration, if eligible (refer to Section 7.4)
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary
- Verify that the subject has fasted for at least 8 hours

  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- PK assessment in participating subjects at select study sites (see Section 9.7.9)
- In preparation for the DEXA bone density scan to be done at the Month 12 visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product (10 mg OCA tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of study medication and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the study medication (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.

9.7.10. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits)
- Assess and record vital signs (height ,weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Subject questionnaires (see Section 12.2.5.1)

- Perform TE (at selected study sites, where available) using the Fibroscan® TE device
- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
- Assess and record AEs
- Review and record concomitant medications
- Assess investigational product compliance and perform investigational product accountability
- Assess for dose titration, if eligible (refer to Section 7.4)
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits
- Obtain urine sample for urinalysis
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks])

Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis.

- Assess and record AEs

- Review and record concomitant medications
- Assess investigational product compliance and perform investigational product accountability
- Assess for dose titration, if eligible (refer to Section 7.4)
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 6 Continued Follow-up Procedures (Semi-annually [±2 weeks])

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure)
- Subject questionnaires (see Section 12.2.5.1)
- Assess and record AEs
- Review and record concomitant medications
- Assess for dose titration, if eligible (refer to Section 7.4)
- Assess investigational product compliance and perform accountability
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Obtain blood samples for:

  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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

9.7.13. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits)
- Assess and record vital signs (height, weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Subject questionnaires (see Section 12.2.5.1)
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device
- Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
- Assess and record AEs
- Review and record concomitant medications
- Assess for dose titration, if eligible (refer to Section 7.4)
- Assess investigational product compliance and perform accountability
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis
- Obtain blood samples for serum chemistry, hematology, and coagulation tests

- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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

9.7.14. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation (withdrawal of consent), an EOT 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 final assessments on or as near as possible to the final day of dosing. In some cases, the subject may discontinue on the day of a scheduled study visit. In these cases, the data will be recorded as EOT procedures in the CRF.

Some assessments noted below may be omitted if they have been completed within the 3 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT Visit:

If possible to do before the visit, when scheduling the EOT visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT Visit:

- Perform a physical examination (including smoking and alcohol consumption habits)
- Assess and record vital signs (height, weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure)

- Perform a standard 12-lead ECG
- Subject questionnaires (see Section 12.2.5.1)
- Perform TE (where available) using the Fibroscan® TE device (not required at EOT if done within 6 months)
- Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved
- Review and record concomitant medications
- Assess investigational product compliance and perform accountability; retrieve used bottles, accordingly, and document returns
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits
- Obtain urine sample for urinalysis
- Obtain blood samples for serum chemistry, hematology, and coagulation tests
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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

The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at controlled room temperature, and protected from excess humidity.

10.4. Investigational Product Preparation

The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of 2 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Liver-related death
- Liver biochemistry (see Table 4 for list of analytes to be tested)
- Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) and ELF, Fibroscan (and others as determined during the course of the study)
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.

11.1.2.1. Non-Invasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF™ test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other

- OCA (and its conjugates) and C4 will be assayed.
- Quality of Life questionnaires.

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
- Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Appendix A 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 13.4) to confirm if they meet the criteria to be considered Clinical Outcome Events.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definition of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject 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.

12.1.1.2. 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-subject 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 subject or may require medical intervention to prevent one of the outcomes listed above

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.2. 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 2. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 2: 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 3, must be entered on the AE CRF. 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 3: Severity of Adverse Events

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

12.1.4. Reporting of Adverse Events and Serious Adverse Events

12.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for

duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

12.1.4.2. 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 medical monitor.

PPD MD, PhD
Telephone: PPD (Pacific time zone)
Mobile: PPD (Pacific time zone)
Email: PPD
SAE Fax: +1 800 497 8521
SAE Email: sae@interceptpharma.com

Alternate Contact:

PPD MD
Tel: PPD (Pacific time zone)
Mobile: PPD
Email: PPD

All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE. SAEs are reported by entering the SAE data into the electronic data capture (EDC) system. Entering the SAE data into the EDC system will automatically notify the medical monitor of the event. In the event that the EDC system is inaccessible, an SAE may be reported by telephone or fax using a paper SAE Report form. 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: subject number and initials, a description of the event, at least one criterion classifying the event as serious and the name and title of the reporting individual. Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities by the Sponsor or designee(s). Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.

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 investigational new drug (IND) safety reports that occur during the study within the time frames required by each regulatory agency.

The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities.

12.1.5. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the medical monitor, 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 subject 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.

12.1.6. 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 medical monitor should be notified immediately (ie, within 24 hours).

All SAEs that occur within 30 days following the cessation of investigational product, whether or not they are related to the study, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.4.2.

12.1.7. 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 subject 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 subject 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 CRF. 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.

12.1.8. 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 and the Sponsor must be notified within 24 hours of the Investigator's learning of the pregnancy by completing the Pregnancy Notification Form and faxing or emailing to the Sponsor at +1 800 497 8521 or sae@interceptpharma.com.

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

The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see Section 8.4.1).

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening visit and at EOT. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Dual Emission X-Ray Absorptiometry

A bone density assessment will be done using the DEXA scan.

12.2.5.1. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their

responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution [Elman 2010]
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects

12.2.6. Laboratory Assessments

Subjects will be instructed to attend each of their study visits (except Screening) in a fasted state, and subjects should remain fasted until their blood samples have been collected. At each visit, the investigator or designee will verify that the subject has fasted for at least 8 hours and record fasting status in the source and CRF. If the subject reports having eaten (water is permitted) within 8 hours, the investigator or designee will document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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. Subjects testing positive for urine drug screen will be excluded from the study.

The list of laboratory analytes to be tested is shown in Table 4.

Table 4: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)

Laboratory Assessment	Analyte
Hematology	Hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, HBE [MCH], MCHC)
Coagulation	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Measurement of Liver Fibrosis	Fibroscan
Bone Density Assessment	DEXA
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Blood Sample for Future Analysis	PBC autoantibodies and other cytokines and interleukins TBD
Other	OCA (parent and conjugates [glyco and tauro]) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.8 through pregnancy outcome.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Randomized Population will include all randomized subjects.
- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria where possible.

13.1.2. Determination of Sample Size

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up.

- 5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

13.1.2.1. Sample Size Re-Estimation Plan

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, starting approximately 2 years after the first subject is randomized, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 121 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.

Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)

- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.11 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3).

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline

as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time to event secondary efficacy analyses will compare randomized OCA versus randomized placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Analyses of changes in MELD score, Child-Pugh score, Mayo Risk Score (MRS), IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN (Corpechot 2011)

- ALP ≤1.67x ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76 x ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, "where no obvious single optimal external control exists, it may be advisable to study multiple external controls". In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is "similar" to a participating subject. The historical database control should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.2).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment.

Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a full range of covariates across which the treatment and historical controls might differ. Although the results of using matching are conditional only on the

observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible.

Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation. Therefore, there is no chance of biasing results in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, hepatocellular carcinoma, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)
- Time to liver transplant or liver-related death
- Time to hepatocellular carcinoma

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.9. Alternative Primary Analysis

Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1). Similar statistical methodology as specified above in Section 13.1.8 for supportive analyses will be utilized.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.10. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

13.1.10.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.10.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.10.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified time point for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.11. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.12. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) based on the ITT population. Subgroups will be assessed at baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.

13.3. Data and Safety Monitoring Committee

An independent DSMC will review safety data at periodic intervals from this study. The DSMC will include internationally recognized hepatologists, pharmaceutical physicians, and a

statistician. All have considerable experience with clinical trial conduct and DSMCs, prior to joining the OCA DSMC. Candidates are screened for conflicts of interest and any candidate found to have such a conflict is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they would be replaced. The DSMC meets approximately quarterly at scheduled meetings and ad hoc meetings are convened, as appropriate. The DSMC reviews all Intercept sponsored Phase 2 and 3 studies. Members of the DSMC will not be allowed to participate as investigators in this study and will not otherwise consult for the Sponsor.

The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1.

The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. The closed minutes will be made available to the Sponsor only after the database is locked.

Data listings provided to the DSMC do not contain individual subject treatment information; however, the DSMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DSMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (MedDRA) coded AE, 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 DSMC in addition to a cumulative list of all SAEs.

The DSMC may request additional analyses if deemed necessary to fulfill the mission of the DSMC. The DSMC will determine if an unscheduled meeting is necessary based on the additional data.

All investigators and responsible IRBs/IECs will be informed of any decisions made by the Sponsor based on recommendations from the DSMC relating to subject safety, which alter the conduct of this study. The investigators will inform the subjects of such actions and the protocol, PIS, and consent will be revised, as appropriate.

13.4. Adjudication Committee

All potential endpoint events will be reviewed by an adjudication committee before inclusion in the any analysis. The adjudication of potential clinical endpoint events will include, but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership,

the reporting of events by the study site, reporting of the final assessment, supply of source documentation to the committee, the review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members will remain blinded to treatment group throughout the study.

In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Seoul Revision, 2008) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, medical monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 medical monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

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

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, clinicaltrials.gov): 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 (when available) 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: The Sponsor, 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.

19. LIST OF REFERENCES

Beuers U, Lindor KD. A major step towards effective treatment evaluation in primary biliary cirrhosis. J Hepatol. 2011 Dec;55(6):1178-80.

Corpechot C, Abenavoli L, Rabahi N, et al. Biochemical response to ursodeoxycholic acid and long term prognosis in primary biliary cirrhosis. Hepatology. 2008 Sep;48(3):871-877.

Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: Biochemical response to treatment and prediction of long-term outcome. J Hepatol 2011;55:1361–1367.

Elman S, Hynan L.S., Gabriel V, and Mayo M.J. The 5-D itch scale: a new measure of pruritus, British Journal of Dermatology 2010 162, pp587–593.

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. J Hepatol. 2009;51:237-267.

Kim WR, Lindor KD, Locke GR, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterol. 2000;119:1631-1636.

Kuiper EM, Hansen BE, de Vries RA, et al. Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid. Gastroenterology. 2009 Apr;136(4):1281-7.

Kumagi T, Guindi M, Fischer SE, et al. Baseline ductopenia and treatment response predict long-term histological progression in primary biliary cirrhosis. Am J Gastroenterol. 2010 Oct;105(10):2186-94.

Lammers WJ, van Buuren HR, Hirschfield GM, et al. Alkaline phosphatase values are a surrogate marker in prediction of transplant-free-survival in patients with primary biliary cirrhosis - an international, collaborative analysis. J Hepatol. 2013; 58(Suppl):S388.

Lindor KD, Gershwin ME, Poupon R, et al. Primary biliary cirrhosis: AASLD Practice Guidelines. Hepatology. 2009;50(1):291-308.

Momah N, Silveira MG, Jorgensen R, et al. Optimizing biochemical markers as endpoints for clinical trials in primary biliary cirrhosis. Liver Int. 2012;32(5):790-795.

APPENDIX A. LIST OF STUDY 747-302 OUTCOME EVENTS

Several of the specified clinical endpoints will also by definition (see Section 12.1) 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 12.1.4). 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

APPENDIX B. LIST OF STUDY 747-302 ANTICIPATED EVENTS

Jaundice

Hepatic decompensation/failure

Hypoalbuminemia

Hyponatremia

Splenomegaly

Hepatorenal syndrome (renal failure in the setting of hepatic failure)

Hepatopulmonary syndrome (pulmonary failure in the setting of hepatic failure)

Fractures

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Original: 03 October 2014

Amendment 1: 29 April 2015

Sponsor

Intercept Pharmaceuticals, Inc.

4760 Eastgate Mall
San Diego, CA 92121

USA

TEL: +1 858 652 6800

FAX: +1 858 558 5961

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD PhD

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

MAY 5 2015
Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigational Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-302. 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 (CRFs) 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor - 24 hour Emergency Reporting

Contact:	PPD MD, PhD, Executive Director, Clinical Research, Intercept Pharmaceuticals, Inc.
Mobile:	PPD (Pacific time zone)
Telephone:	PPD
Email:	PPD
SAE Fax:	+1 800 497 8521
SAE Email:	sae@interceptpharma.com

Or if Not Available:

Contact:	PPD MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.
Telephone:	PPD (Pacific time zone)
Mobile:	PPD
Email:	PPD

Clinical Operations and Project Management

Contact:	PPD PPD Clinical Operations, Intercept Pharmaceuticals, Inc.
Telephone:	PPD (Pacific time zone)
Mobile:	PPD
Fax:	PPD
Email:	PPD

2. SYNOPSIS

Name of Sponsor/Company: Intercept Pharmaceuticals, Inc.

Name of Investigational Product: Obeticholic Acid (OCA)

Name of Active Ingredient: OCA; 6α-ethyl chenodeoxycholic acid (6-ECDCA); INT-747

Title of Study: A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Study Number: 747-302

Study Center(s): Approximately 170 investigational study sites, globally

Study Period (Years): The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

Number of Subjects (planned): Approximately 350 subjects

Phase of Study: Phase 3b

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cirrhosis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the pharmacokinetics of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

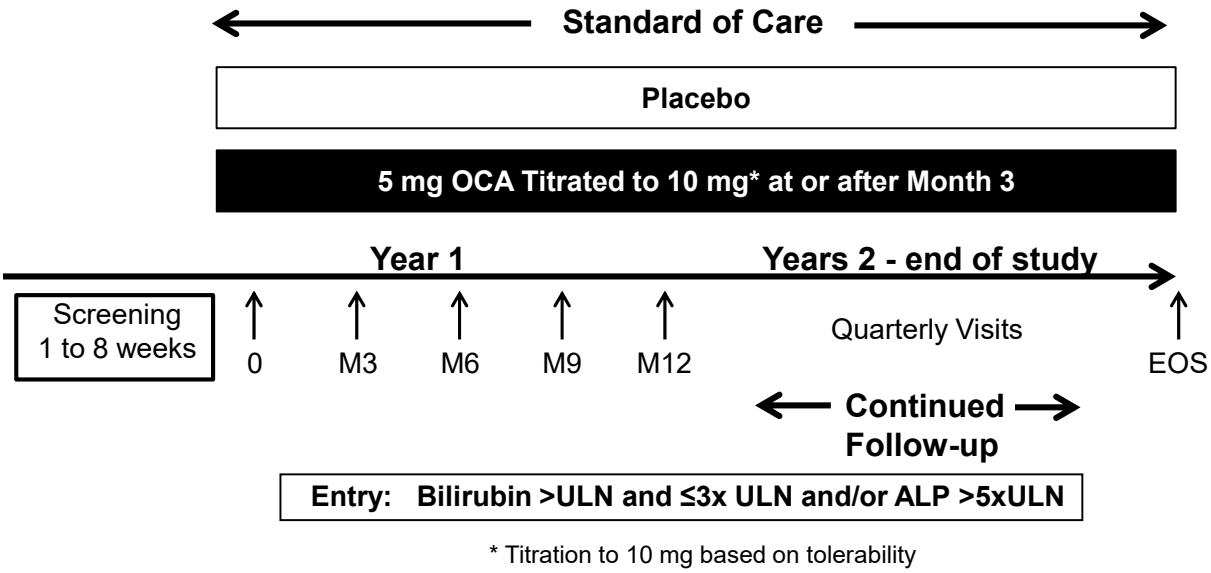
To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).

Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.

Schematic Diagram:



EOS = end of study; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤3x ULN and/or a mean ALP >5x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects 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:

- Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or
- Intrauterine device (IUD); 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 subject)

6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     - Variceal bleed
     - Uncontrolled ascites
     - Encephalopathy
     - Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 μmol/L)

3. Mean total bilirubin >3x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Placebo (matching tablets)

Duration of Treatment:

It is estimated that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 121 total primary endpoint events.

Duration of Subject Participation:

It is estimated that subject participation will be a minimum of approximately 6 years.

Criteria for Evaluation:

Primary Objectives	Assessments
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Change in baseline liver biochemistry	Liver biochemistry (see Table 5 for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhance liver fibrosis (ELF), and Fibroscan®
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
Pharmacokinetics	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events Clinical laboratory values

Statistical Methods:

Sample Size Justification

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up
- 5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Randomized, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Every event for enrolled subjects will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory.

Other Efficacy Analyses

The following secondary efficacy analyses will compare OCA to placebo on time to the following events:

- Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above)
- Development of varix/varices
- Liver-related death
- Liver-related death or liver transplant
- Liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Further details on efficacy, health outcomes, and pharmacokinetic analyses are specified in Section 13.

Safety Analysis

Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will compare OCA and placebo using the Safety Population.

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

LIST OF TABLES

LIST OF FIGURES

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
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DEXA	dual-emission X-ray absorptiometry
DSMC	Data Safety Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhance liver fibrosis
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
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
HDL	high density lipoprotein
IB	Investigational Brochure

Abbreviation or Specialist Term	Explanation
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
LDL	low density lipoprotein
LTSE	Long-term safety extension
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cirrhosis
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
the Sponsor	Intercept Pharmaceuticals, Inc.
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
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 Primary Biliary Cirrhosis and Obeticholic Acid

Primary Biliary Cirrhosis (PBC) 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, is currently the only treatment approved for PBC (Lindor 2009). While UDCA therapy has a marked effect on the treatment of PBC, up to 50% of patients show a suboptimal response or no response to UDCA. Such patients are at significantly increased risk of a poor clinical outcome due to PBC disease progression. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]). Obeticholic acid (OCA) is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary human bile acid chenodeoxycholic acid (CDCA). OCA is currently being developed in the United States (US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (27 Jul 2010) for the treatment of PBC.

5.2. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment. 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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects 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 10 mg OCA 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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rational for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. Starting subjects on 5 mg OCA and titrating to 10 mg based on the clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Doses

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.

Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.

5.5.2.2. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Summary of Known Potential Risks with OCA

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, but with a much lower frequency than that observed in subjects 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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).

Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

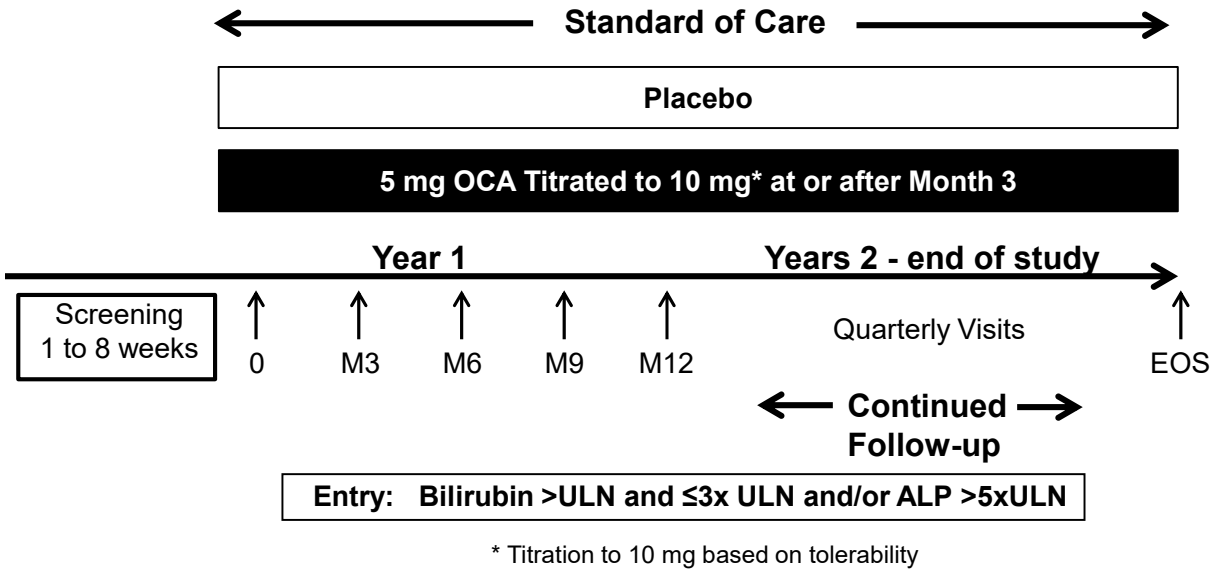
This is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤3x ULN or ALP >5x. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 350 subjects meeting all enrollment criteria will be recruited into the study over an approximate 2-year period, randomly allocated to treatment with either OCA or matching placebo once daily in a 1:1 ratio. Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). Investigational product will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. The randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used. Following 3 months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability. It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 121 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Safety Monitoring Committee; DSMC) terminates the study.

This study will be conducted at up to approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

	Year 1								Years 2 through End of Study				
	Screening Visit 1[a]	**Screening Visit 2[a]**	**Day 0**	**Safety Contact[b]**	**M 3**	**M 6**	**M 9**	**M 12**	**M 3 continued follow-up**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[c]**
Visit Windows (+/-)[d]	**3 to 8 wks prior to Day 0**	**1 to 6 wks prior to Day 0**		**±1 wk**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**
STUDY PROCEDURES													
Informed Consent	X												
Medical/PBC History[e]	X												
Inclusion/Exclusion Criteria	X	X	X										
Physical Exam	X							X[e]				X[e]	X
Vital Signs (including weight)	X[f]		X		X	X	X	X[f]		X		X[f]	X[f]
12-Lead Electrocardiogram	X												X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X			X		X		X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS) [g]			X					X				X	X
TE Fibroscan®/DEXA[h]			X					X				X	X
Endoscopy[i]			X					X				X	
Hepatic Ultrasound[j]			X					X				X	X
Physical Exam and Assessments for Mayo Risk and Child-Pugh Scores[k]			X			X		X		X		X	X
Adverse Events	X	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	X
Health Outcome Assessments [l]			X		X	X	X	X	X	X	X	X	X
Randomization/Treatment Assigned			X										

Table 1: Schedule of Study Procedures (Continued)

	Year 1								Years 2 through End of Study				
	Screening Visit 1[a]	**Screening Visit 2[a]**	**Day 0**	**Safety Contact[b]**	**M 3**	**M 6**	**M 9**	**M 12**	**M 3 continued follow-up**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[c]**
Visit Windows (+/-)[d]	**3 to 8 wks prior to Day 0**	**1 to 6 wks prior to Day 0**		**±1 wk**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**
Dose Titration (if applicable)[m]					X								
Dispense Investigational Product[n]			X		X	X	X	X	X	X	X	X	
IP Accountability/Compliance				X	X	X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS[o]													
Urinalysis	X		X					X				X	X
Urine-based β-hCG Pregnancy Test[p]	X		X										
Chemistry/Hematology/Coagulation	X	X[a]	X		X	X	X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X		X	X	X[q]	X				X	X
Markers of Hepatic Fibrosis and/or Inflammation[r]			X			X		X		X		X	X
Genetics[s]			X					X				X	
Blood Sample for Future Analysis[t]			X			X		X		X		X	X

β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF = fibroblast growth factor-19; FIS= Fatigue Impact Score; IP = Investigational Product; M = month, wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have 2 ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 (± 1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.

[c] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[d] Visits should be based on Day 0 (not on the prior visit).

[e] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[f] Height will be collected at this visit.

[g] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).

[h] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.

[i] Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.4 for additional information related to the allowed window at Day 0 for this specific procedure.
[j] Ultrasound will be conducted to enhance HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for this specific procedure
[k] 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 case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
[l] Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.
[m] After 3 months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
[n] Subject to begin dosing on Day 1
[o] The subject should be instructed to fast overnight (at least 8 hours) prior to each visit (except Screening Visit 1). Fasting is required prior to all study visits, but water is permitted.
[p] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at the central laboratory. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
[q] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.9 for the PK sampling schedule.
[r] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.
[s] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12
[t] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 350 subjects will be randomized in the study to achieve 121 adjudicated primary endpoint events.

7.3. Treatment Assignment

Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3-month study visit or at any study visit thereafter depending on tolerability.

7.4. Dose Titration Criteria

After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the 3-month visit or any study visit following the 3-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.

7.4.1. Safety Criteria for Adjustment or Stopping Doses

Investigational product may be temporarily decreased (ie, from 10 mg to 5 mg daily, or by alternate day dosing) 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 (5 mg or 10 mg) once the issues relating to the lack of tolerability are resolved.

Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.

7.5. Criteria for Study Termination

The Sponsor 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 DSMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 121 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.
2. A mean total bilirubin >ULN and ≤3x ULN and/or a mean ALP >5x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects 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:
   - Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or
   - Intrauterine device (IUD); 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 subject)

6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy
     – Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 μmol/L)
3. Mean total bilirubin >3x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.

8.4. Subject Withdrawal from Investigational Product or Study Criteria

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

If a female subject becomes pregnant, she must discontinue taking investigational product, but should continue with the study visit schedule. The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes pregnancy is not considered an AE. The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.

8.4.2. Other Reasons for Discontinuation of Investigational Product

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).

The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination and the study will only terminate at the time when the needed number of adjudicated events has accrued (or at the discretion of the Sponsor):

- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important.
- Withdrawal of consent
  - Consent may be fully withdrawn
  - 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 potential adjudicated hepatic and/or cardiovascular events.

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.

8.4.2.1. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.2.2. Lost to Follow-up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.3. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

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: placebo and OCA. Investigational product will be administered orally, once daily for the duration of the study. Each dose will be made up of 1 tablet (ie, one 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, once daily. Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time each day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

9.1.1. Dose Adjustment Beginning at Month 3

After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Subjects taking bile acid sequestrants (BAS) 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).

PBC Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. Subjects that discontinue investigational product but continue commercial OCA therapy are expected to continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).

9.3. Treatment Compliance

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

Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable, follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2, below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the

subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.

Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

9.5. Assignment of Site and Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 3 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0. The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening visit 1 interval is 3 to 8 weeks prior to Day 0. Screening visit 2 interval is 1 to 6 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Months 3-12	±2 week (14 days)
Quarterly visits (Months 15 – EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study.

EOT = end of treatment EOS = end of study

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 2 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected. Subjects who

do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned.

Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN and/or an ALP >5x ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.
- Assess and record any pretreatment-emergent AEs.
- Record current concomitant medications.
- Verify that the subject has fasted for at least 8 hours.

  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.
- In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate.

9.7.4. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device. If TE has been done within 6 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
- Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc),

the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.

– Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.

- 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 Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- 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.
- Randomize the subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- 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 tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhance liver fibrosis [ELF])

  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Access the IWRS and dispense investigational product.
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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.

9.7.5. Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone]):

- Assess and record AEs.
- Review and record concomitant medications.
- Assess investigational product compliance.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 3 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF

  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Schedule the next visit and assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 6 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Verify that the subject has fasted for at least 8 hours.

  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.8. Month 9 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- PK assessment in participating subjects at select study sites (see Section 9.7.9).
- In preparation for the DEXA bone density scan to be done at the Month 12 visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Following collection of the Month 9 fasted samples (refer to Section 9.7.8 , subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of study medication and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the study medication (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.10. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).
- Assess and record vital signs (height ,weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device.

- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks])

- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 6 Continued Follow-up Procedures (Semi-annually [±2 weeks])

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema

  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance and perform accountability.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
  - Blood sample for future analysis (refer to Section 11.1.2.3).
- At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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

9.7.13. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Assess and record vital signs (height, weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).

- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device.
- Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance and perform accountability.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)

  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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.

9.7.14. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 2) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject 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 and EOS procedures in the CRF.

Table 2: 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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contactb	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review onlyb	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

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

[b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.6.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Assess and record vital signs (height, weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (where available) using the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).
- Conduct a DEXA bone density scan (selected study sites; not required at EOT/EOS if done within 6 months); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- 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 and perform accountability; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)

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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline (and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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

The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at controlled room temperature, and protected from excess humidity.

10.4. Investigational Product Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15

- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of 2 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Liver-related death
- Liver biochemistry (see Table 5 for list of analytes to be tested)
- Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) and ELF, Fibroscan (and others as determined during the course of the study).
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Non-Invasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF™ test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other

- OCA (and its conjugates) and C4 will be assayed.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
  - Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
- Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Appendix A 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 13.4) to confirm if they meet the criteria to be considered Clinical Outcome Events.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definition of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject 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.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.2. 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 3. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 3: 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 4, must be entered on the AE CRF. 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 4: Severity of Adverse Events

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

12.1.4. Reporting of Adverse Events and Serious Adverse Events

12.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

12.1.4.2. 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 medical monitor.

PPD MD, PhD
Telephone: PPD (Pacific time zone)
Mobile: PPD (Pacific time zone)
Email: PPD
SAE Fax: +1 800 497 8521
SAE Email: sae@interceptpharma.com

Alternate Contact:

PPD MD
Tel: PPD (Pacific time zone)
Mobile: PPD
Email: PPD

All SAEs occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE. SAEs are reported by entering the SAE data into the electronic data capture (EDC) system. Entering the SAE data into the EDC system will automatically notify the medical monitor of the event. In the event that the EDC system is inaccessible, an SAE may be reported by telephone or fax using a paper SAE Report form. 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: subject number and initials, a description of the event, at least one criterion classifying the event as serious and the name and title of the reporting individual. Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities by the Sponsor or designee(s). Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.

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. A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR). The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities.

12.1.5. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the medical monitor, 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 subject 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.

12.1.6. 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 medical monitor should be notified immediately (ie, within 24 hours).

All SAEs that occur within 30 days following the cessation of investigational product, whether or not they are related to the study, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.4.2.

SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.

12.1.7. 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 subject 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 subject 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 CRF. 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.

12.1.8. 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 and the Sponsor must be notified within 24 hours of the Investigator's learning of the pregnancy by completing the Pregnancy Notification Form and faxing or emailing to the Sponsor at +1 800 497 8521 or sae@interceptpharma.com.

Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use of investigational product.

The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see Section 8.4.1).

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening visit 1 and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Dual Emission X-Ray Absorptiometry

A bone density assessment will be done using the DEXA scan.

12.2.6. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.7. Laboratory Assessments

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

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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 5.

Table 5: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[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, HBE [MCH], MCHC)
Coagulation	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Measurement of Liver Fibrosis	Fibroscan
Bone Density Assessment	DEXA
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Blood Sample for Future Analysis	PBC autoantibodies and other cytokines and interleukins TBD
Other	OCA (parent and conjugates [glyco and tauro]) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.8 through pregnancy outcome.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Randomized Population will include all randomized subjects.
- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as

baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria where possible.

13.1.2. Determination of Sample Size

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up.
- 5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

13.1.2.1. Sample Size Re-Estimation Plan

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, starting approximately 2 years after the first subject is randomized, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 121 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this

modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.

Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be

conducted as specified in Section 13.1.11 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3).

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time to event secondary efficacy analyses will compare randomized OCA versus randomized placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Analyses of changes in MELD score, Child-Pugh score, Mayo Risk Score (MRS), IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67x ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76 x ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, “where no obvious single optimal external control exists, it may be advisable to study multiple external controls”. In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is “similar” to a participating subject. The historical database control

should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.2).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment.

Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a full range of covariates across which the treatment and historical controls might differ. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible.

Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation. Therefore, there is no chance of biasing results in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, hepatocellular carcinoma, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)

- Time to liver transplant or liver-related death
- Time to hepatocellular carcinoma

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.9. Alternative Primary Analysis

Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1). Similar statistical methodology as specified above in Section 13.1.8 for supportive analyses will be utilized.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.10. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

13.1.10.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.10.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.10.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified time point for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.11. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.12. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) based on the ITT population. Subgroups will be assessed at baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.

13.3. Data and Safety Monitoring Committee

An independent DSMC will review safety data at periodic intervals from this study. The DSMC will include internationally recognized hepatologists, pharmaceutical physicians, and a statistician. All have considerable experience with clinical trial conduct and DSMCs, prior to joining the OCA DSMC. Candidates are screened for conflicts of interest and any candidate found to have such a conflict is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they would be replaced. The DSMC meets approximately quarterly at scheduled meetings and ad hoc meetings are convened, as appropriate. The DSMC reviews all Intercept sponsored Phase 2 and 3 studies. Members of the DSMC will not be allowed to participate as investigators in this study and will not otherwise consult for the Sponsor.

The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study.

The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.

Data listings provided to the DSMC do not contain individual subject treatment information; however, the DSMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DSMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (MedDRA) coded AE, 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 DSMC in addition to a cumulative list of all SAEs.

The DSMC may request additional analyses if deemed necessary to fulfill the mission of the DSMC. The DSMC will determine if an unscheduled meeting is necessary based on the additional data.

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

13.4. Adjudication Committee

All potential endpoint events will be reviewed by an adjudication committee before inclusion in the any analysis. The adjudication of potential clinical endpoint events will include, but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership, the reporting of events by the study site, reporting of the final assessment, supply of source documentation to the committee, the review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members will remain blinded to treatment group throughout the study.

In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, local applicable regulatory requirements (in addition to Appendix C), and the Sponsor's policies.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, medical monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 medical monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, clinicaltrials.gov): 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 (when available) 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: The Sponsor, 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.

19. LIST OF REFERENCES

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APPENDIX A. LIST OF STUDY 747-302 OUTCOME EVENTS

Several of the specified clinical endpoints will also by definition (see Section 12.1) 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 12.1.4). 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

APPENDIX B. LIST OF STUDY 747-302 ANTICIPATED EVENTS

Jaundice

Hepatic decompensation/failure

Hypoalbuminemia

Hyponatremia

Splenomegaly

Hepatorenal syndrome (renal failure in the setting of hepatic failure)

Hepatopulmonary syndrome (pulmonary failure in the setting of hepatic failure)

Fractures

APPENDIX C. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: xx April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact**:** PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD	Contact**:** PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2

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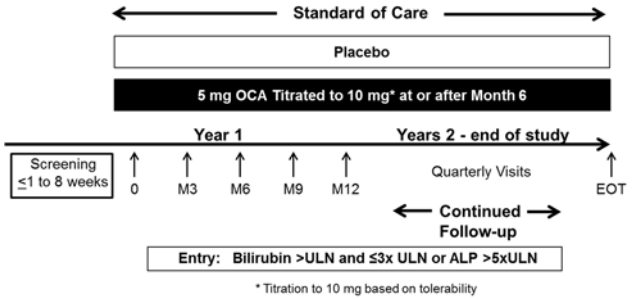
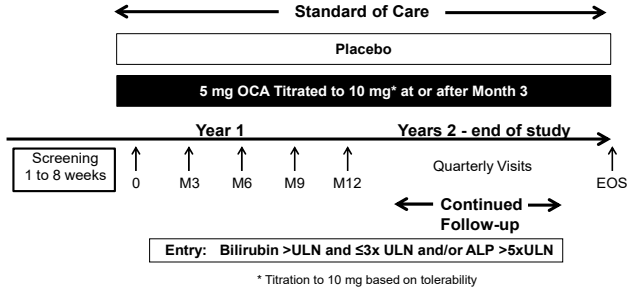
	weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

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Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN **and/**or **a mean** ALP >5x ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12.	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria

3. Mean total bilirubin >3x ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. Deleted text</td></tr>
<tr><td>Synopsis</td><td><u>Criteria for Evaluation:</u><table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td><u>Criteria for Evaluation:</u><table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td><u>Statistical Methods: Other Efficacy Analyses</u>
• Added text</td><td><u>Statistical Methods: Other Efficacy Analyses</u>
• Development of varix/varices</td></tr>
<tr><td>4</td><td><u>List of Abbreviations</u>
Added text</td><td><u>List of Abbreviations</u><table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy</td></tr>
</table>

Section	Original Text	Revised Text
	subjects. As of 31 **March 2014**, **a total of 1023** subjects have received at least **one** dose of OCA and of these, **414 (40%)** were subjects with PBC. 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 **up to 4 years.** The **LSTE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete	subjects. As of 31 **January 2015**, **approximately 1650** subjects have received at least **1** dose of OCA and of these, **432** were subjects with PBC **with ≤5 years of OCA treatment**. 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**.** The **LTSE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete
5.5.2.1	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group*	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to

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	Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.**
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects

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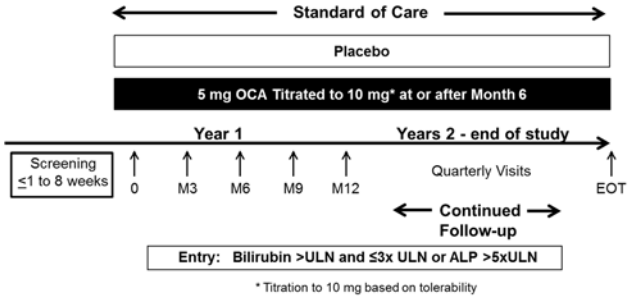
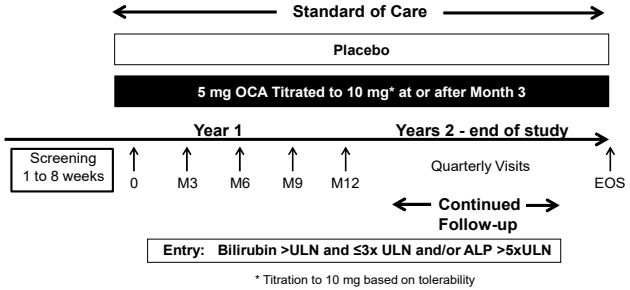
	manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)*** ***Visit Window ≤1 to 8 wks …*** ***Visit window in 2nd column added new text*** ***Added text***	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now* ***"Screening Visit 1"*** *2nd column now* ***Screening Visit 2*** ***3*** *to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3***

Section	Original Text	Revised Text
	Footnote a: All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on ALP (ALP >5x ULN),** the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3x ULN).** *Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed *Footnote e:* Medical history at Screening will smoking and alcohol consumption history and current habits for both. *Footnote g:* **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1) *Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. *Footnote i:* ***Added text*** *Footnote j*: ***Added text***	*Footnote a* All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**. *Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(± 1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed. *Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both. *Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6) *Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.** *Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.** *Footnote j*: **Ultrasound will be conducted to enhance HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to**

Section	Original Text	Revised Text
	Footnote k: ***Added text***	**Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote l: ***Added text***	*Footnote k:* **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 case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.
	Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
		Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change
7.3	Treatment Assignment	Treatment Assignment

Section	Original Text	Revised Text
	Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN **and**/or **a mean** ALP >5x ULN

Section	Original Text	Revised Text
	4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3x ULN**

Section	Original Text	Revised Text
	4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) 5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	**4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** **5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent. The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text***	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures)**. The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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**

Section	Original Text	Revised Text
		allow continued access to medical records to assess for potential adjudicated hepatic and/or cardiovascular events The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
	The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	Concomitant Medications 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 CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then

Section	Original Text	Revised Text
	investigational product should be discontinued to avoid potential double dosing.	investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).**
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.

9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.** **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
		Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.
9.6	Restrictions **No additional restrictions.**	Restrictions **Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment
</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
<tr><td>EOS
(When subject terminates the study)</td><td>The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject’s</td></tr>
</table>
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</table>

Section	Original Text	Revised Text
		participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study. EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**.	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart

Section	Original Text	Revised Text
	• For subjects that do not qualify based on ALP alone (ALP >5x ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN).	• For subjects that do not qualify based on ALP alone (ALP >5x ULN), the mean of **all available (at least 2; including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs**

Section	Original Text	Revised Text
		• **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours** – **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits** • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the**

Section	Original Text	Revised Text
		screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should**

Section	Original Text	Revised Text
		also be performed when platelet counts are <150 x 10^9 /L.
	• ***Added text***	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• ***Added text***	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**
9.7.6	Month 3 Procedures	Month 3 Procedures

Section	Original Text	Revised Text
	• *Added text* • *Added text*	• **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:** – **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • *Added text*	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • *Added text*	Month 9 Procedures • **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**
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.8), subjects who are participating in the PK assessment

Section	Original Text	Revised Text
	will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** ○ **Presence/absence of peripheral edema** ○ **Presence (degree)/absence of ascites**

Section	Original Text	Revised Text
		○ **Presence (degree)/absence of hepatic encephalopathy**
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1)	Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

Section	Original Text	Revised Text
	• *Added text*	• Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

Section	Original Text	Revised Text
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 2) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.**
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
		[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.6.
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing. Prior to the EOT Visit: During the EOT Visit: • Subject questionnaires (see Section 12.2.6) • Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable • ***Added text*** • ***Added text*** • ***Added text***	Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing Prior to the EOT/**EOS** Visit: During the EOT/**EOS** Visit • Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)** • Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable • Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6) • Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months) • Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• *Added text*	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline**

Section	Original Text	Revised Text
		(and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of

Section	Original Text	Revised Text
	• *Added text*	outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:** **a. PBC-40: The PBC-40 (Jacoby 2005) 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.** **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).**

Section	Original Text	Revised Text
		c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
12.1.1.2	Serious Adverse Event • ***Added text***	Serious Adverse Event **Events <u>not</u> 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**

Section	Original Text	Revised Text
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Section	Original Text	Revised Text
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 List of Laboratory Analytes to be Tested
<table>
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<tr><td>Serum Chemistry</td><td>Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to** Appendix C**)** and the Sponsor's policies.
19	List of References • Added text	List of References **Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83.** **Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.** **Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629.** **Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.**
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Original: 03 October 2014

Amendment 1: 29 April 2015

Amendment 1.1: 12 November 2015

EudraCT Number: 2014-005012-42

Sponsor

Intercept Pharmaceuticals, Inc.

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San Diego, CA 92121

USA

TEL: +1 858 652 6800

FAX: +1 858 558 5961

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD , PhD

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

12 NOV 2015

Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigational Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-302. 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 (CRFs) 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor - 24 hour Emergency Reporting

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SAE Email:	sae@interceptpharma.com

Or if Not Available:

Contact:	PPD MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.
Telephone:	PPD (Pacific time zone)
Email:	PPD

Clinical Operations and Project Management

Contact:	PPD PPD Clinical Operations, Intercept Pharmaceuticals, Inc.
Telephone:	PPD (Pacific time zone)
Mobile:	PPD
Fax:	PPD
Email:	PPD

2. SYNOPSIS

Name of Sponsor/Company: Intercept Pharmaceuticals, Inc.

Name of Investigational Product: Obeticholic Acid (OCA)

Name of Active Ingredient: OCA; 6α-ethyl chenodeoxycholic acid (6-ECDCA); INT-747

Title of Study: A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Study Number: 747-302

Study Center(s): Approximately 170 investigational study sites, globally

Study Period (Years): The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

Number of Subjects (planned): Approximately 350 subjects

Phase of Study: Phase 3b

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cirrhosis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the pharmacokinetics of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

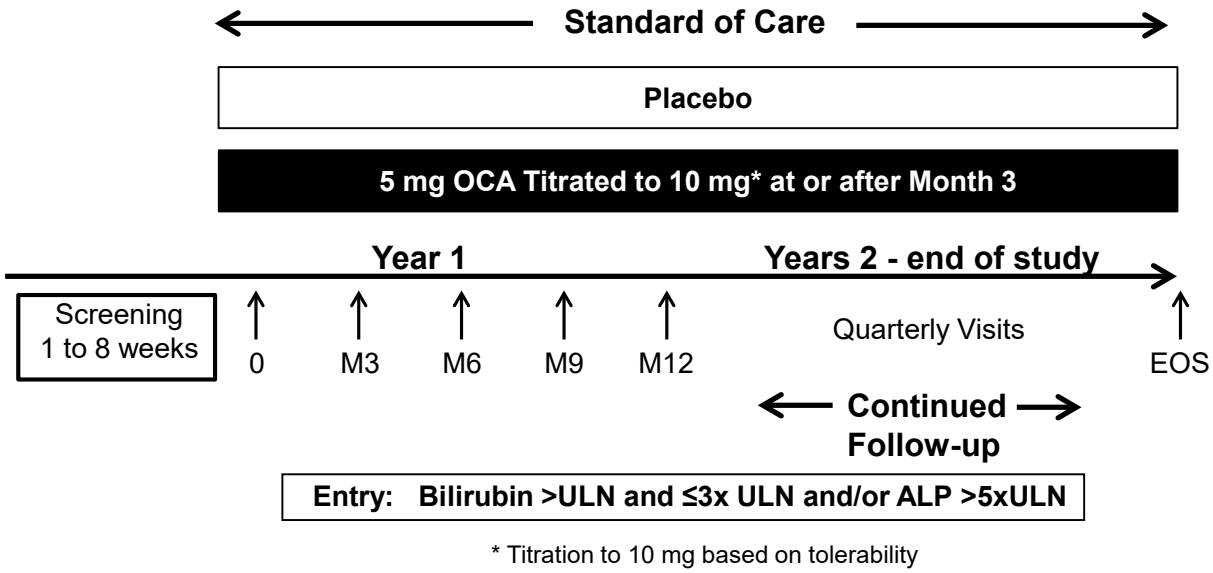
To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN).

Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.

Schematic Diagram:



EOS = end of study; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤3x ULN and/or a mean ALP >5x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects 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:

- Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or
- Intrauterine device (IUD); 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 subject)

6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     - Variceal bleed
     - Uncontrolled ascites
     - Encephalopathy
     - Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 μmol/L)

3. Mean total bilirubin >3x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
14. UDCA naïve (unless contraindicated)

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Placebo (matching tablets)

Duration of Treatment:

It is estimated that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 121 total primary endpoint events.

Duration of Subject Participation:

It is estimated that subject participation will be a minimum of approximately 6 years.

Criteria for Evaluation:

Primary Objectives	Assessments
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Change in baseline liver biochemistry	Liver biochemistry (see Table 5 for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhance liver fibrosis (ELF), and Fibroscan®
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
Pharmacokinetics	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events Clinical laboratory values

Statistical Methods:

Sample Size Justification

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Randomized, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Every event for enrolled subjects will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory.

Other Efficacy Analyses

The following secondary efficacy analyses will compare OCA to placebo on time to the following events:

- Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above)
- Development of varix/varices
- Liver-related death
- Liver-related death or liver transplant
- Liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Further details on efficacy, health outcomes, and pharmacokinetic analyses are specified in Section 13.

Safety Analysis

Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will compare OCA and placebo using the Safety Population.

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

LIST OF TABLES

LIST OF FIGURES

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
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DEXA	dual-emission X-ray absorptiometry
DSMC	Data Safety Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhance liver fibrosis
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
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
HDL	high density lipoprotein
IB	Investigational Brochure

Abbreviation or Specialist Term	Explanation
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
LDL	low density lipoprotein
LTSE	Long-term safety extension
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cirrhosis
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
the Sponsor	Intercept Pharmaceuticals, Inc.
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
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 Primary Biliary Cirrhosis and Obeticholic Acid

Primary Biliary Cirrhosis (PBC) 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, is currently the only treatment approved for PBC (Lindor 2009). While UDCA therapy has a marked effect on the treatment of PBC, up to 50% of patients show a suboptimal response or no response to UDCA. Such patients are at significantly increased risk of a poor clinical outcome due to PBC disease progression. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]). Obeticholic acid (OCA) is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary human bile acid chenodeoxycholic acid (CDCA). OCA is currently being developed in the United States (US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (27 Jul 2010) for the treatment of PBC.

5.2. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment. 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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects 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 10 mg OCA 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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rational for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. Starting subjects on 5 mg OCA and titrating to 10 mg based on the clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Doses

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.

Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.

5.5.2.2. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Summary of Known Potential Risks with OCA

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, but with a much lower frequency than that observed in subjects 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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).

Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

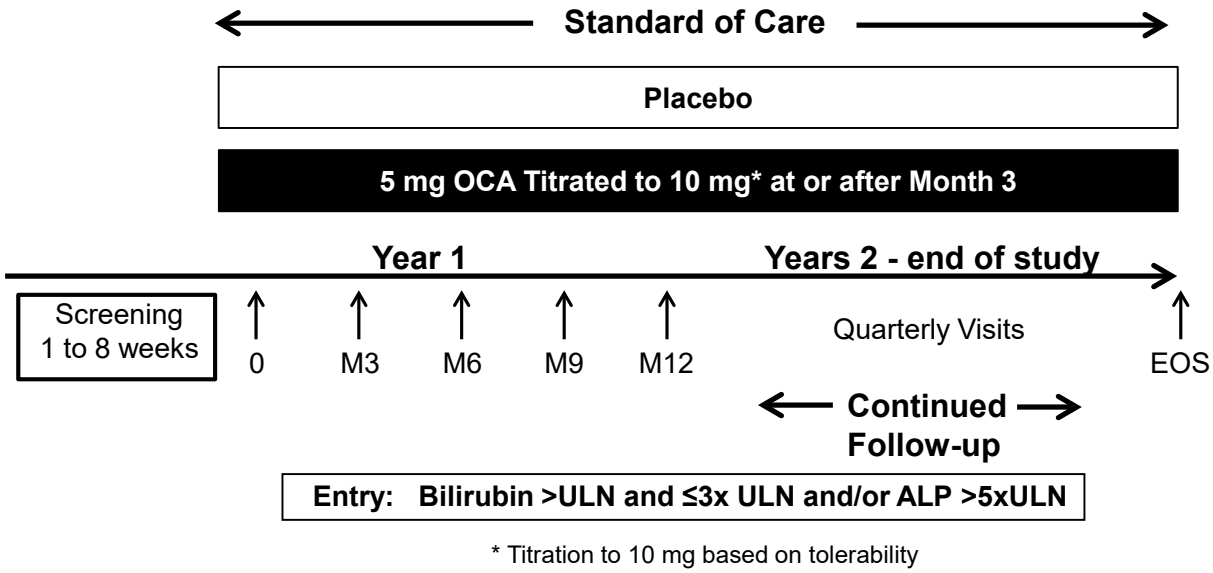
This is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤3x ULN or ALP >5x. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 350 subjects meeting all enrollment criteria will be recruited into the study over an approximate 2-year period, randomly allocated to treatment with either OCA or matching placebo once daily in a 1:1 ratio. Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). Investigational product will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. The randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used. Following 3 months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability. It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 121 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Safety Monitoring Committee; DSMC) terminates the study.

This study will be conducted at up to approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

	Year 1								Years 2 through End of Study				
	Screening Visit 1[a]	**Screening Visit 2[a]**	**Day 0**	**Safety Contact[b]**	**M 3**	**M 6**	**M 9**	**M 12**	**M 3 continued follow-up**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[c]**
Visit Windows (+/-)[d]	**3 to 8 wks prior to Day 0**	**1 to 6 wks prior to Day 0**		**±1 wk**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**
STUDY PROCEDURES													
Informed Consent	X												
Medical/PBC History[e]	X												
Inclusion/Exclusion Criteria	X	X	X										
Physical Exam	X							X[e]				X[e]	X
Vital Signs (including weight)	X[f]		X		X	X	X	X[f]		X		X[f]	X[f]
12-Lead Electrocardiogram	X												X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X			X		X		X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS) [g]			X					X				X	X
TE Fibroscan®/DEXA[h]			X					X				X	X
Endoscopy[i]			X					X				X	
Hepatic Ultrasound[j]			X					X				X	X
Physical Exam and Assessments for Mayo Risk and Child-Pugh Scores[k]			X			X		X		X		X	X
Adverse Events	X	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	X
Health Outcome Assessments [l]			X		X	X	X	X	X	X	X	X	X
Randomization/Treatment Assigned			X										

Table 1: Schedule of Study Procedures (Continued)

	Year 1								Years 2 through End of Study				
	Screening Visit 1[a]	**Screening Visit 2[a]**	**Day 0**	**Safety Contact[b]**	**M 3**	**M 6**	**M 9**	**M 12**	**M 3 continued follow-up**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[c]**
Visit Windows (+/-)[d]	**3 to 8 wks prior to Day 0**	**1 to 6 wks prior to Day 0**		**±1 wk**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**	**±2 wks**
Dose Titration (if applicable)[m]					X								
Dispense Investigational Product[n]			X		X	X	X	X	X	X	X	X	
IP Accountability/Compliance				X	X	X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS[o]													
Urinalysis	X		X					X				X	X
Urine-based β-hCG Pregnancy Test[p]	X		X										
Chemistry/Hematology/Coagulation	X	X[a]	X		X	X	X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X		X	X	X[q]	X				X	X
Markers of Hepatic Fibrosis and/or Inflammation[r]			X			X		X		X		X	X
Genetics[s]			X					X				X	
Blood Sample for Future Analysis[t]			X			X		X		X		X	X

β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF = fibroblast growth factor-19; FIS= Fatigue Impact Score; IP = Investigational Product; M = month, wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have 2 ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 (±1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.

[c] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[d] Visits should be based on Day 0 (not on the prior visit).

[e] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[f] Height will be collected at this visit.

[g] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).

[h] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.

[i] Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.4 for additional information related to the allowed window at Day 0 for this specific procedure.
[j] Ultrasound will be conducted to enhance HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for this specific procedure
[k] 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 case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
[l] Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.
[m] After 3 months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
[n] Subject to begin dosing on Day 1
[o] The subject should be instructed to fast overnight (at least 8 hours) prior to each visit (except Screening Visit 1). Fasting is required prior to all study visits, but water is permitted.
[p] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at the central laboratory. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
[q] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.9 for the PK sampling schedule.
[r] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.
[s] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12
[t] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 350 subjects will be randomized in the study to achieve 121 adjudicated primary endpoint events.

7.3. Treatment Assignment

Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3-month study visit or at any study visit thereafter depending on tolerability.

7.4. Dose Titration Criteria

After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the 3-month visit or any study visit following the 3-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.

7.4.1. Safety Criteria for Adjustment or Stopping Doses

Investigational product may be temporarily decreased (ie, from 10 mg to 5 mg daily, or by alternate day dosing) 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 (5 mg or 10 mg) once the issues relating to the lack of tolerability are resolved.

Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.

7.5. Criteria for Study Termination

The Sponsor 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 DSMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 121 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.
2. A mean total bilirubin >ULN and ≤3x ULN and/or a mean ALP >5x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects 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:
   - Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or
   - Intrauterine device (IUD); 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 subject)

6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     - Variceal bleed
     - Uncontrolled ascites
     - Encephalopathy
     - Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 μmol/L)
3. Mean total bilirubin >3x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
14. UDCA naïve (unless contraindicated)

8.4. Subject Withdrawal from Investigational Product or Study Criteria

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

If a female subject becomes pregnant, she must discontinue taking investigational product, but should continue with the study visit schedule. The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes pregnancy is not considered an AE. The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.

8.4.2. Other Reasons for Discontinuation of Investigational Product

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination

procedures should only be conducted if the subject withdraws consent (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).

The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination and the study will only terminate at the time when the needed number of adjudicated events has accrued (or at the discretion of the Sponsor):

- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important.
- Withdrawal of consent
  - Consent may be fully withdrawn
  - 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 potential adjudicated hepatic and/or cardiovascular events.

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.

8.4.2.1. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.2.2. Lost to Follow-up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.3. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in

the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

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: placebo and OCA. Investigational product will be administered orally, once daily for the duration of the study. Each dose will be made up of 1 tablet (ie, one 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, once daily. Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time each day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

9.1.1. Dose Adjustment Beginning at Month 3

After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Subjects taking bile acid sequestrants (BAS) 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).

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, 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.

PBC Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. Subjects that discontinue investigational product but continue commercial OCA therapy are expected to continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).

9.3. Treatment Compliance

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

Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable, follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2, below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.

Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

9.5. Assignment of Site and Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 3 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (±2 weeks) following Day 0. The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening visit 1 interval is 3 to 8 weeks prior to Day 0. Screening visit 2 interval is 1 to 6 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Months 3-12	±2 week (14 days)
Quarterly visits (Months 15 – EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study.

EOS = end of study EOT = end of treatment

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 2 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned.

Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN and/or an ALP >5x ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.
- Assess and record any pretreatment-emergent AEs.
- Record current concomitant medications.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.
- In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate.

9.7.4. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device. If TE has been done within 6 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit

window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.

- Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
  - Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.
- 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 Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- 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.
- Randomize the subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- 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 tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhance liver fibrosis [ELF])
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Access the IWRS and dispense investigational product.
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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.

9.7.5. Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone]):

- Assess and record AEs.
- Review and record concomitant medications.
- Assess investigational product compliance.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 3 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Schedule the next visit and assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 6 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.

  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.8. Month 9 Procedures

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- PK assessment in participating subjects at select study sites (see Section 9.7.9).
- In preparation for the DEXA bone density scan to be done at the Month 12 visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Following collection of the Month 9 fasted samples (refer to Section 9.7.8 , subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of study medication and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the study medication (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.10. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).

- Assess and record vital signs (height ,weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device.
- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:

  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks])

- Assess and record AEs.
- Review and record concomitant medications.
- 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 and perform investigational product accountability.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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. Month 6 Continued Follow-up Procedures (Semi-annually [±2 weeks])

- Assess and record vital signs (weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance and perform accountability.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
  - Blood sample for future analysis (refer to Section 11.1.2.3).
- At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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

9.7.13. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Assess and record vital signs (height, weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device.
- Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance and perform accountability.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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, 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.

9.7.14. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 2) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject 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 and EOS procedures in the CRF.

Table 2: 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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[b]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

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

[b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.6.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Assess and record vital signs (height, weight, oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Subject and Quality of Life questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (where available) using the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).
- Conduct a DEXA bone density scan (selected study sites; not required at EOT/EOS if done within 6 months); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.
  - Presence/absence of peripheral edema
  - Presence (degree)/absence of ascites
  - Presence (degree)/absence of hepatic encephalopathy
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- 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 and perform accountability; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)

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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline (and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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

The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at controlled room temperature, and protected from excess humidity.

10.4. Investigational Product Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15

- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of 2 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Liver-related death
- Liver biochemistry (see Table 5 for list of analytes to be tested)
- Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) and ELF, Fibroscan (and others as determined during the course of the study).
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Non-Invasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF™ test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other

- OCA (and its conjugates) and C4 will be assayed.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
  - Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
- Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Appendix A 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 13.4) to confirm if they meet the criteria to be considered Clinical Outcome Events.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definition of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject 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.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.2. 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 3. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 3: 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 4, must be entered on the AE CRF. 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 4: Severity of Adverse Events

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

12.1.4. Reporting of Adverse Events and Serious Adverse Events

12.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

12.1.4.2. 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 medical monitor.

PPD MD, PhD
Telephone: PPD (Pacific time zone)
Email: PPD
SAE Fax: +1 800 497 8521
SAE Email: sae@interceptpharma.com

Alternate Contact:

PPD MD
Tel: PPD (Pacific time zone)
Mobile: PPD
Email: PPD

All SAEs occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE. SAEs are reported by entering the SAE data into the electronic data capture (EDC) system. Entering the SAE data into the EDC system will automatically notify the medical monitor of the event. In the event that the EDC system is inaccessible, an SAE may be reported by telephone or fax using a paper SAE Report form. 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: subject number and initials, a description of the event, at least one criterion classifying the event as serious and the name and title of the reporting individual. Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities by the Sponsor or designee(s). Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.

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. A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR). The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities.

12.1.5. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the medical monitor, 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 subject 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.

12.1.6. 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 medical monitor should be notified immediately (ie, within 24 hours).

All SAEs that occur within 30 days following the cessation of investigational product, whether or not they are related to the study, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.4.2.

SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.

12.1.7. 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 subject 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 subject 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 CRF. 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.

12.1.8. 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 and the Sponsor must be notified within 24 hours of the Investigator's learning of the pregnancy by completing the Pregnancy Notification Form and faxing or emailing to the Sponsor at +1 800 497 8521 or sae@interceptpharma.com.

Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use of investigational product.

The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see Section 8.4.1).

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening visit 1 and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Dual Emission X-Ray Absorptiometry

A bone density assessment will be done using the DEXA scan.

12.2.6. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.7. Laboratory Assessments

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

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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 5.

Table 5: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[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, HBE [MCH], MCHC)
Coagulation	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Measurement of Liver Fibrosis	Fibroscan
Bone Density Assessment	DEXA
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Blood Sample for Future Analysis	PBC autoantibodies and other cytokines and interleukins TBD
Other	OCA (parent and conjugates [glyco and tauro]) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.8 through pregnancy outcome.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Randomized Population will include all randomized subjects.
- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as

baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria where possible.

13.1.2. Determination of Sample Size

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

13.1.2.1. Sample Size Re-Estimation Plan

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, starting approximately 2 years after the first subject is randomized, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 121 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.

Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.11 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the

OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3).

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time to event secondary efficacy analyses will compare randomized OCA versus randomized placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Analyses of changes in MELD score, Child-Pugh score, Mayo Risk Score (MRS), IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67x ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76 x ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, “where no obvious single optimal external control exists, it may be advisable to study multiple external controls”. In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is “similar” to a participating subject. The historical database control

should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.2).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment.

Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a full range of covariates across which the treatment and historical controls might differ. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible.

Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation. Therefore, there is no chance of biasing results in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, hepatocellular carcinoma, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)

- Time to liver transplant or liver-related death
- Time to hepatocellular carcinoma

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.9. Alternative Primary Analysis

Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1). Similar statistical methodology as specified above in Section 13.1.8 for supportive analyses will be utilized.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.10. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

13.1.10.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.10.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.10.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified time point for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.11. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.12. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) based on the ITT population. Subgroups will be assessed at baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.

13.3. Data and Safety Monitoring Committee

An independent DSMC will review safety data at periodic intervals from this study. The DSMC will include internationally recognized hepatologists, pharmaceutical physicians, and a statistician. All have considerable experience with clinical trial conduct and DSMCs, prior to joining the OCA DSMC. Candidates are screened for conflicts of interest and any candidate found to have such a conflict is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they would be replaced. The DSMC meets approximately quarterly at scheduled meetings and ad hoc meetings are convened, as appropriate. The DSMC reviews all Intercept sponsored Phase 2 and 3 studies. Members of the DSMC will not be allowed to participate as investigators in this study and will not otherwise consult for the Sponsor.

The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study.

The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.

Data listings provided to the DSMC do not contain individual subject treatment information; however, the DSMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DSMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (MedDRA) coded AE, 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 DSMC in addition to a cumulative list of all SAEs.

The DSMC may request additional analyses if deemed necessary to fulfill the mission of the DSMC. The DSMC will determine if an unscheduled meeting is necessary based on the additional data.

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

13.4. Adjudication Committee

All potential endpoint events will be reviewed by an adjudication committee before inclusion in the any analysis. The adjudication of potential clinical endpoint events will include, but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership, the reporting of events by the study site, reporting of the final assessment, supply of source documentation to the committee, the review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members will remain blinded to treatment group throughout the study.

In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, local applicable regulatory requirements (in addition to Appendix C), and the Sponsor's policies.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, medical monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 medical monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, clinicaltrials.gov): 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 (when available) 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: The Sponsor, 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.

19. LIST OF REFERENCES

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Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005 Nov;54(11):1622-9.

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APPENDIX A. LIST OF STUDY 747-302 OUTCOME EVENTS

Several of the specified clinical endpoints will also by definition (see Section 12.1) 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 12.1.4). 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

APPENDIX B. LIST OF STUDY 747-302 ANTICIPATED EVENTS

Jaundice

Hepatic decompensation/failure

Hypoalbuminemia

Hyponatremia

Splenomegaly

Hepatorenal syndrome (renal failure in the setting of hepatic failure)

Hepatopulmonary syndrome (pulmonary failure in the setting of hepatic failure)

Fractures

APPENDIX C. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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Online-Only Content: Audio podcast is available at www.jama.com.

APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

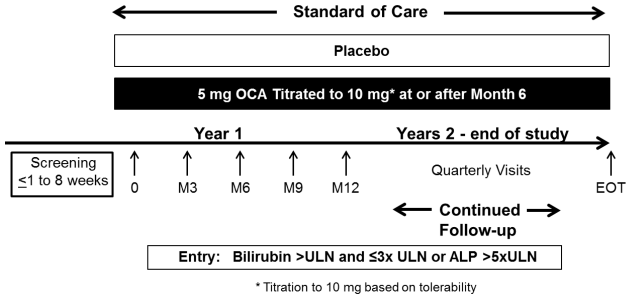
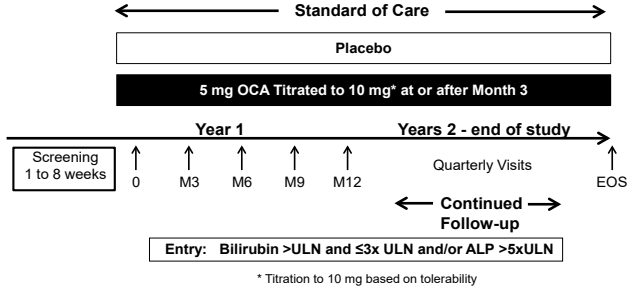
Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: xx April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact**:** PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD	Contact**:** PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available**

Section	Original Text	Revised Text
	randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	**screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN **and**/or **a mean** ALP >5x ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0

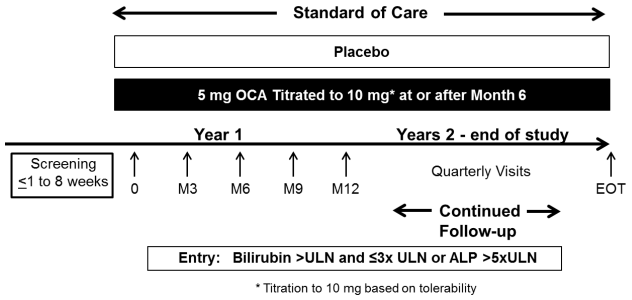
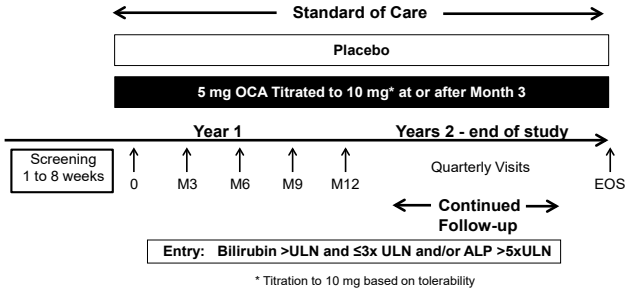
Section	Original Text	Revised Text
	5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** **4.** Other medical conditions that may diminish life expectancy to **<2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3x ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. Deleted text</td></tr>
<tr><td>Synopsis</td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td>Statistical Methods: Other Efficacy Analyses
• Added text</td><td>Statistical Methods: Other Efficacy Analyses
• Development of varix/varices</td></tr>
<tr><td>4</td><td>List of Abbreviations
Added text</td><td>List of Abbreviations<table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC.

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 up to 4 years. The LSTE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment.

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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete</td></tr>
<tr><td>5.5.2.1</td><td>Rationale for OCA Doses
… The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment</td><td>Rationale for OCA Doses
… The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6</td></tr>
</table>

Section	Original Text	Revised Text
	groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects**

Section	Original Text	Revised Text
		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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)***	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now **"Screening Visit 1"*** *2nd column now **Screening Visit 2***

Section	Original Text	Revised Text
	Visit Window ≤1 to 8 wks … ***Visit window in 2nd column added new text*** ***Added text***	***3** to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3***
	Footnote a: All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on ALP (ALP >5x ULN),** the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3x ULN).** *Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed *Footnote e:* Medical history at Screening will smoking and alcohol consumption history and current habits for both. *Footnote g:* **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1)	*Footnote a*: All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**. *Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(±1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed. *Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both. *Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6)

Section	Original Text	Revised Text
	Footnote h: Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.	*Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote i: ***Added text***	*Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote j: ***Added text***	*Footnote j*: **Ultrasound will be conducted to enhance HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote k: ***Added text***	*Footnote k:* **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 case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.**
	Footnote l: ***Added text***	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.

Section	Original Text	Revised Text
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally). ***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally). ***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***
7.3	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**

Section	Original Text	Revised Text
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN or an ALP >5x ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3x ULN **and/**or **a mean** ALP >5x ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**

Section	Original Text	Revised Text
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** 4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) 5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3x ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** **5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent.	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures)**.

Section	Original Text	Revised Text
	The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text*** The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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 potential adjudicated hepatic and/or cardiovascular events** The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded	Concomitant Medications 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

Section	Original Text	Revised Text
	in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.14 Early Discontinuation and/or Early Termination Procedures).**
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.

Section	Original Text	Revised Text
9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.** **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.6</td><td>Restrictions
No additional restrictions.</td><td>Restrictions
Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.</td></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
</td></tr>
</table>

Section	Original Text	Revised Text
		EOS (When subject terminates the study) — **The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study.** EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**.	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart

Section	Original Text	Revised Text
	• For subjects that do not qualify based on ALP alone (ALP >5x ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN).	• For subjects that do not qualify based on ALP alone (ALP >5x ULN), the mean of **all available (at least 2; including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3x ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs** • **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours** – **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and**

Section	Original Text	Revised Text
		remind the subject that fasting is required prior to all study visits • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** • Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment**

Section	Original Text	Revised Text
		DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
	• *Added text*	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are <150 x 10^9 /L.**
	• *Added text*	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**

Section	Original Text	Revised Text
	• ***Added text***	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• ***Added text***	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**
9.7.6	Month 3 Procedures • ***Added text*** • ***Added text***	Month 3 Procedures • **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:** – **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • ***Added text***	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites**

Section	Original Text	Revised Text
		– **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • ***Added text***	Month 9 Procedures • **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**
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.8), subjects who are participating in the PK assessment will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.**

Section	Original Text	Revised Text
		• **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** - **Presence/absence of peripheral edema** - **Presence (degree)/absence of ascites** - **Presence (degree)/absence of hepatic encephalopathy**
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** - **Presence/absence of peripheral edema** - **Presence (degree)/absence of ascites** - **Presence (degree)/absence of hepatic encephalopathy** • **Review and record any non-study related medical or surgical treatment procedures and any medically**

Section	Original Text	Revised Text
		relevant HCP or non-HCP related office visits that have occurred since the previous study visit
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** - **Presence/absence of peripheral edema** - **Presence (degree)/absence of ascites** - **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

Section	Original Text	Revised Text
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 2) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.**
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.	[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.6. Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing
	Prior to the EOT Visit:	Prior to the EOT/**EOS** Visit:
	During the EOT Visit: • Subject questionnaires (see Section 12.2.6) • Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable	During the EOT/**EOS** Visit • Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)** • Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
	• ***Added text***	• Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6)
	• ***Added text***	• Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months)
	• ***Added text***	• Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• *Added text*	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline (and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN),**

Section	Original Text	Revised Text
		subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications. • ***Added text***	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:**

Section	Original Text	Revised Text
		a. PBC-40: The PBC-40 (Jacoby 2005) 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. **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).** **c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)**
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

Section	Original Text	Revised Text
12.1.1.2	Serious Adverse Event • *Added text*	Serious Adverse Event **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**
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the

Section	Original Text	Revised Text
		submissions to IRBs and health authorities must be retained in the appropriate study file(s).
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to** Appendix C**)** and the Sponsor's policies.

Section	Original Text	Revised Text
19	List of References • Added text	List of References **Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83.** **Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.** **Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629.** **Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.**
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 (DATED 12 NOV 2015)

Rationale

The changes to Amendment 1 of the protocol, detailed below, include an additional exclusion criteria and changes to text precluding UDCA naïve subjects from entering the study and clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, thus answering questions raised by regulatory authorities.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1.1. (Note: Revised text in Amendment 1.1 is indicated in bold font, and the text deleted from Protocol Amendment 1 is crossed out in the table below. Minor formatting changes are not listed.)

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
Title Page	Original: 03 October 2014 Amendment 1: 29 APRIL 2015	Original: 03 October 2014 Amendment 1: 29 **April** 2015 **Amendment 1.1: 12 November 201**
Study Personnel Contact Information	~~Mobile:~~ PPD ~~(Pacific time zone)~~ Telephone: PPD ~~Telephone~~ PPD	(deleted) Telephone: PPD (deleted)
Synopsis, Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
Synopsis, Statistical Methods: Sample Size Justification	• ~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)
8.3 Subject Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
9.2 Concomitant Medications	(insertion)	**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, showed weak effect**

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
		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.
12.1.4.2 Reporting of Serious Adverse Event	~~Mobile: PPD (Pacific time zone)~~ Telephone: +1 ~~858 964 1571~~	(deleted) Telephone: PPD
13.1.2 Determination of Sample Size	~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

The COBALT Study

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Version 3: 07 September 2016

EudraCT Number: 2014-005012-42

Sponsor

Intercept Pharmaceuticals, Inc.

4760 Eastgate Mall
San Diego, CA 92121

USA

TEL: +1 858 250 6398

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD PhD

Sept 7, 2016

Date

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigational Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-302. 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 (CRFs) 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor – 24-hour Emergency Reporting

Contact:	PPD MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.
Mobile:	PPD
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Email:	PPD
SAE Fax:	+1 800 497 8521
SAE Email:	sae@interceptpharma.com

Or if Not Available:

Contact:	PPD MD, PhD, Executive Director, Clinical Research, Intercept Pharmaceuticals, Inc.
Telephone:	PPD
Mobile:	PPD (Pacific time zone)
Email:	PPD

Clinical Operations and Project Management

Contact:	PPD PPD Clinical Operations, Intercept Pharmaceuticals, Inc.
Telephone:	PPD (Pacific time zone)
Mobile:	PPD
Fax:	PPD
Email:	PPD

2. SYNOPSIS

Name of Sponsor/Company: Intercept Pharmaceuticals, Inc.

Name of Investigational Product: Obeticholic Acid (OCA)

Name of Active Ingredient: OCA; 6α-ethyl chenodeoxycholic acid (6-ECDCA); INT-747

Title of Study: A Phase 3b, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cirrhosis

Study Number: 747-302

Study Center(s): Approximately 170 investigational study sites, globally

Study Period (Years): The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

Number of Subjects (planned): Approximately 350 subjects

Phase of Study: Phase 3b

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cirrhosis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the pharmacokinetics of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

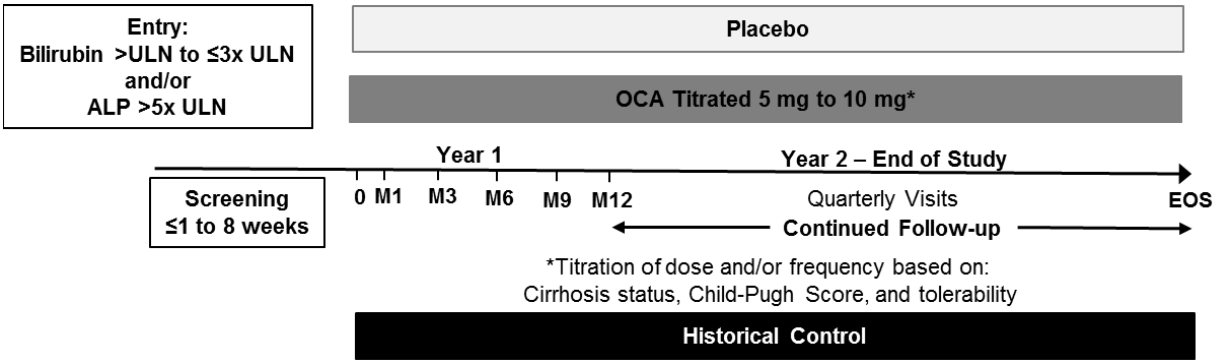
To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened twice during a 1 to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.6).

Investigational product will be taken orally, once daily for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (> upper limit of normal [ULN]/ ≤ ULN).

Schematic Diagram:



EOS = end of study; ULN = upper limit of normal
Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:

- Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a

maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.

- For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.
- Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability.

Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Planned Dosing Regimen		
	Standard	**Modified**	
	Non-Cirrhotic/ Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly	5 mg twice weekly
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly	10 mg twice weekly
Titration 3 [b] (≥6 weeks after Titration 2)	NA	5 mg daily	NA

[a] Starting dose based on subject's cirrhosis status and Child-Pugh Score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤3× ULN and/or a mean ALP >5× ULN

3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects 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:
   - Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or
   - Intrauterine device (IUD); 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 subject
6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites

  - Encephalopathy
  - Spontaneous bacterial peritonitis
- Known or suspected hepatocellular carcinoma
- Prior transjugular intrahepatic portosystemic shunt procedure
- Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 μmol/L)

3. Mean total bilirubin >3× ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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-month 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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
14. UDCA naïve (unless contraindicated)

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Placebo (matching tablets)

Duration of Treatment:

It is estimated that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 121 total primary endpoint events.

Duration of Subject Participation:

It is estimated that subject participation will be a minimum of approximately 6 years.

Criteria for Evaluation:

Primary Objectives	**Assessments**
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Change in baseline liver biochemistry	Liver biochemistry (see Table 10: for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhance liver fibrosis (ELF), and Fibroscan®
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
Pharmacokinetics	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events Clinical laboratory values

Statistical Methods:

Sample Size Justification

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Randomized, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

Every event for enrolled subjects will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory.

Other Efficacy Analyses

The following secondary efficacy analyses will compare OCA to placebo on time to the following events:

- Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above)
- Development of varix/varices
- Liver-related death
- Liver-related death or liver transplant
- Liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Further details on efficacy, health outcomes, and pharmacokinetic analyses are specified in Section 13.

Safety Analysis

Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will compare OCA and placebo using the Safety Population.

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

LIST OF TABLES

LIST OF FIGURES

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
CAC	Cardiovascular Adjudication Committee
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DEXA	dual-emission X-ray absorptiometry
DMC	Data Monitoring Committee
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhance liver fibrosis
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FIS	Fatigue Impact Scale
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid

Abbreviation or Specialist Term	Explanation
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
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
LDL	low density lipoprotein
LTSE	Long-term safety extension
MACE	Major adverse cardiovascular events
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PSC	primary sclerosing cholangitis
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SUSAR	suspected unexpected serious adverse reactions
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
the Sponsor	Intercept Pharmaceuticals, Inc.

Abbreviation or Specialist Term	Explanation
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 Primary Biliary Cirrhosis and Obeticholic Acid

Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis) 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, is currently the only treatment approved for PBC (Lindor 2009). While UDCA therapy has a marked effect on the treatment of PBC, up to 50% of patients show a suboptimal response or no response to UDCA. Such patients are at significantly increased risk of a poor clinical outcome due to PBC disease progression. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]). Obeticholic acid (OCA) is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary human bile acid chenodeoxycholic acid (CDCA). OCA is currently being developed in the United States (US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication.

5.2. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 31 Jan 2016, approximately 1726 subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 458 subjects had PBC, 330 subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease (NAFLD), 33 subjects had alcoholic cirrhosis/portal hypertension, and 20 subjects 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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects reaching specific criteria for ALP and bilirubin (ALP $<1.67\times$ upper limit of normal [ULN] with a $\geq 15\%$ reduction

and bilirubin ≤ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to <1.67× 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 10 mg OCA 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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rationale for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. As a result, starting subjects on 5 mg OCA and titrating to 10 mg based on tolerability and clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Doses

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Based on these data, the indicated commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.

5.5.2.2. Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh Score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).

5.5.2.3. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Summary of Known Potential Risks with OCA

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, but with a much lower frequency than that observed in subjects 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 subjects 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 above 10 mg OCA. 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 (HDL) and an increase in low density lipoprotein (LDL). Notably, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤3× ULN or ALP >5× ULN. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 350 subjects meeting all enrollment criteria will be recruited into the study over an approximate 2-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). Subjects will be screened during a 1 to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.6). Randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used.

Investigational product will be taken orally, once daily. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo. Following 3 months of once daily treatment with investigational product, the dose should be titrated to a maximum 10 mg OCA or matching placebo once daily, based on tolerability (see Section 7.3).

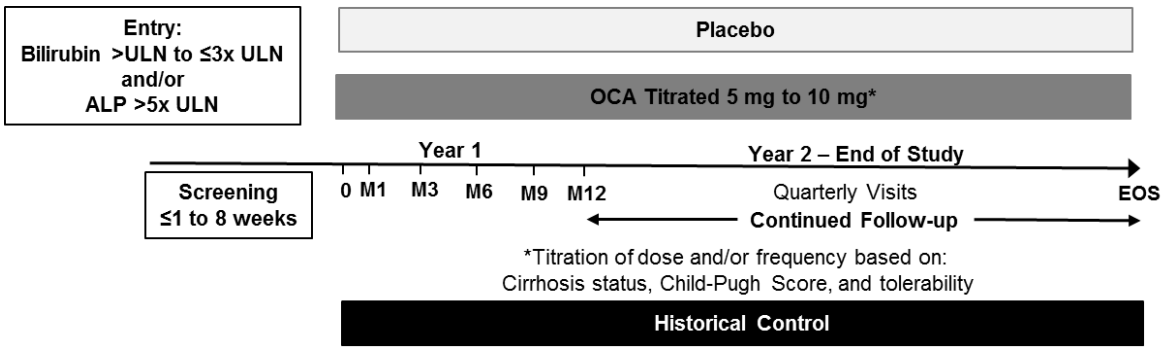
Subjects with cirrhosis (see Section 9.7.3) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.

It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 121 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.

This study will be conducted at approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; ULN = upper limit of normal
Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2)

	Screening Visits		Day 0	M 1	M 3	1-Month Post-Titration Visit[b]	M 6	M 9	M 12
	1	2[a]							
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Informed Consent	X								
Medical/PBC History[d]	X								
Cirrhosis Status Assessment[e]	X								
Inclusion/Exclusion Criteria	X	X	X						
Physical Exam	X								X[d]
Assessments for Mayo Risk Score[f]	X						X		X
Assessments for Child-Pugh Score[g]	X				X		X	X	X
Vital Signs (including weight)	X[h]		X		X		X	X	X[h]
12-Lead Electrocardiogram	X								X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X				X		X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[i]			X						X
TE Fibroscan®/DEXA[j]			X						X
Endoscopy[k]			X						X
Hepatic Ultrasound[l]		X							X
Adverse Events	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Health Outcome Assessments[m]			X		X		X	X	X
Randomization/Treatment Assigned			X						
Dose Titration: Standard Dosing[n,o]					X		X (if applicable)		
Dose Titration: Modified Dosing (if applicable)[n,o]					X		X	X	X

Table 1: Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2) (Continued)

	Screening Visits		Day 0	M 1	M 3	1-Month Post-Titration Visit[b]	M 6	M 9	M 12
	1	2[a]							
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Dispense Investigational Product[p]			X		X		X	X	X
IP Accountability/Compliance				X	X	X	X	X	X
Dosing Diary			X	X	X	X	X	X	X
LABORATORY EVALUATIONS[q]									
Urinalysis	X		X						X
Urine-based β-hCG Pregnancy Test[r]	X		X						
Chemistry/Hematology/ Coagulation	X	X[a]	X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X		X		X	X[s]	X
Markers of Hepatic Fibrosis and/or Inflammation[t]			X				X		X
Genetics[u]			X						X
Blood Sample for Future Analysis[v]			X				X		X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] Post-Titration visits must be performed 1 month (+ 1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.

[f] Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.

[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] Height will be collected at this visit.

[i] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).

[j] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.

[k] Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed window at Day 0 for this specific procedure.

[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: If a lesion is found, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.

[m] Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[n] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[o] Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh Score (Section 9.7.4). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

[p] Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

[q] The subject 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.

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

[s] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.13 for the PK sampling schedule.

[t] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.

[v] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

Table 2: Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)

	Year 2 through End of Study					
	M 3 continued follow-up	**1-Month Post-Titration Visit[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**+1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Physical Exam[d]					X	X
Assessment for Mayo Risk Score[e]			X		X	X
Assessments for Child-Pugh Scores[f]	X		X	X	X	X
Vital Signs (including weight)			X		X[g]	X[g]
12-Lead Electrocardiogram					X	X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[h]					X	X
TE Fibroscan®/DEXA[i]					X	X
Endoscopy[j]					X	
Hepatic Ultrasound[k]					X	X
Adverse Events	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Health Outcome Assessments[l]	X		X	X	X	X
Dose Titration (if applicable)[m,n]	X		X	X	X	
Dispense Investigational Product	X		X	X	X	
IP Accountability/Compliance	X	X	X	X	X	X
Dosing Diary	X	X	X	X	X	X
LABORATORY EVALUATIONS[o]						
Urinalysis					X	X
Chemistry/Hematology/Coagulation	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)					X	X
Markers of Hepatic Fibrosis and/or Inflammation[p]			X		X	X

Table 2: Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2) (Continued)

	Year 2 through End of Study					
	M 3 continued follow-up	**1-Month Post-Titration Visit[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**+1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Genetics[q]					X	
Blood Sample for Future Analysis[r]			X		X	X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency. Post-titration visits must be performed 1 month ± 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment.

[b] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] The yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.

[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 case report form.

[g] Height will be collected at this visit.

[h] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).

[i] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Not required if done within 6 months of visit.

[j] Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices.

[k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: If a lesion is found, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.

[l] Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[m] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[n] Dose Titration is based on cirrhosis status (see Section 9.7.3) and Child-Pugh Score (Section 9.7.4). The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

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

[p] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[q] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.

[r] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 121 primary endpoint events, estimated to be approximately 8 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 350 subjects will be randomized in the study to achieve 121 adjudicated primary endpoint events.

7.3. Planned Dosing Regimen

Subjects will be randomized to treatment with either OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.

Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5 mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).

For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.

Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Scheduled Dosing Regimen		
	Standard	**Modified[d]**	
	Non-Cirrhotic/ Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Starting Dose[a] (Day 0)	5 mg daily	5 mg once weekly	5 mg once weekly
Titration 1[b] (≥Month 3)	10 mg daily	5 mg twice weekly[c]	5 mg twice weekly[c]
Titration 2[b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly[c]	10 mg twice weekly[c]
Titration 3[b] (≥6 weeks after Titration 2)	NA	5 mg daily	NA

[a] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4).
[c] Dosing per the twice weekly schedule must be at least 3 days apart.
[d] Refer to Appendix A for additional instructions regarding subjects following the Modified Dosing Regimen.

The dosing regimen should be determined as described in Table 4. Investigators should follow the dosing/titration schedule as shown in Table 3.

Table 4: Determination of Dosing Regimen

Cirrhosis?	No	Yes	Yes	Yes
Child-Pugh Score	Any	A	B	C
Dosing Regimen	Standard		Modified for Child-Pugh B	Modified for Child-Pugh C

7.4. Dose Titration 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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh Score.

Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability; see Section 7.4.2).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due to changes in cirrhosis or Child-Pugh 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.

Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score

Original Status	New Status[a]		
	Non-cirrhotic *OR* Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Non-cirrhotic *or* Child-Pugh A	*No Change*	10 mg daily → 5 mg daily 5 mg daily →No change **or** 10 mg twice weekly[b]	5 mg or 10 mg daily → 10 mg twice weekly[b]
Child-Pugh B	5 mg daily → 10 mg daily	*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	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 subject begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.3 or Appendix A.

[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the Investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).

Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).

Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.

Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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.

Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in study medication (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.

To be eligible for a dose up-titration:

- Subjects 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.
- There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required.

7.4.2. Safety Criteria for Adjustment or Stopping Doses

Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.

7.5. Criteria for Study Termination

The Sponsor 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 DMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at

an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 121 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.
2. A mean total bilirubin >ULN and ≤3× ULN and/or a mean ALP >5× ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects 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:
   - Double-barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or

- Intrauterine device (IUD); 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 subject)

6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy
     – Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)
3. Mean total bilirubin >3× ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
14. UDCA naïve (unless contraindicated)

8.4. Subject Withdrawal from Investigational Product or Study

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

If a female subject becomes pregnant, she must discontinue taking investigational product, but should continue with the study visit schedule. The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes pregnancy is not considered an AE. The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.

8.4.2. Other Reasons for Discontinuation of Study or Investigational Product

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule

through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).

The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination and the study will only terminate at the time when the needed number of adjudicated events has accrued (or at the discretion of the Sponsor):

- Subject begins treatment with commercially available OCA
- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- 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 subject 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 potential adjudicated hepatic and/or cardiovascular events.

Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.

8.4.2.1. 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. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.4. Lost to Follow-up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.5. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.18, Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or matching 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 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, up to once daily, for the duration of the study.

All subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Drug Interactions

Subjects 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 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 Investigator's Brochure (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 with OCA that may be observed in study subjects.

PBC Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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. Subjects who continue with commercial OCA therapy must discontinue study

medication and are expected to continue through the end of the study (see Section 7.4.2). The study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (see Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).

9.3. Treatment Compliance

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

Subjects should be instructed to complete a dosing diary to help monitor compliance to the prescribed dosing regimen. Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable, follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to one of two treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2, below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects 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 subject). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the subject'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 subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The Data Monitoring Committee (DMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded subject data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the trial 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 Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0. The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening Visit 1 interval is 3 to 8 weeks prior to Day 0. Screening Visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Month 1	+1 week (7 days)
Titration Visit – Standard Dosing Regimen	≥Month 3
Titration Visit 1 – Modified Dosing Regimen	≥Month 3
Titration Visit 2 – Modified Dosing Regimen	≥6 weeks after Titration Visit 1
Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY)	≥6 weeks after Titration Visit 2
Post-Titration Visit	1 month (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency
Month 3 to Month 12	±2 weeks (14 days)
Quarterly visits (Months 15 to EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study.

EOS = end of study; EOT = end of treatment

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Assessing Cirrhosis

To determine which dosing regimen subjects should follow, the presence or absence of 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 is defined as a subject 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)

Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A, Section 7.3, Table 3 and Table 4).

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. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh 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. It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen.

Table 6: 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)

9.7.5. Mayo Risk Score

Mayo Risk Score (MRS) (Dickson 1989) is calculated and reported within the EDC system based on data entered into the eCRF. Calculation of MRS includes investigator assessment of peripheral edema and the use of diuretic therapy, which will be assessed during adverse event and concomitant medicine review at the scheduled visits and entered into the eCRF, as well as total bilirubin, albumin, and prothrombin time results obtained from the central laboratory data.

9.7.6. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 week to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 3 weeks to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 week to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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.

Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN and/or an ALP >5× ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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
- Assess for the presence/absence of cirrhosis.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score
- Perform assessment for calculation of Mayo Risk Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.
- Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.

- Assess and record any pretreatment-emergent AEs.
- Record current concomitant medications.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.
- In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate.

9.7.7. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device. If TE has been done within 6 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc), the procedure may be completed within the screening visit window, at Screening Visit 1 (if data is needed for cirrhosis assessment) or as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.

- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
- Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
  - Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- 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 subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- 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 tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhance liver fibrosis [ELF])

  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Access the IWRS and dispense investigational product
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 1 Procedures:

- Assess and record AEs
- Review and record concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:
  - At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Month 1 visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.
  - If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Month 1 visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- 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.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Post-Titration Visit Procedures:

- Assess and record AEs.
- Review and record concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration visit requirements:
  - At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.
  - If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 6 Procedures

- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).

- Subject questionnaires (see Section 12.2.6)
- Assess and record AEs.
- Review and record concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.12. Month 9 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- 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.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- PK assessment in participating subjects at select study sites (see Section 9.7.13).
- In preparation for the DEXA bone density scan to be done at the Month 12 visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.13. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA

exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule.

Following collection of the Month 9 fasted samples (refer to Section 9.7.12, subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of study medication and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the study medication (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4-hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink with no other food allowed until after the final 6-hour post-dose sample is collected. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.14. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires and (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device.
- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).

- Assess and record AEs.
- Review and record concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.15. Month 3 and Month 9 Continued Follow-Up Procedures (±2 weeks)

- Perform assessments for calculation of Child-Pugh Score.
- Assess and record AEs.
- Review and record concomitant medications.

- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.16. Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])

- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.

- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
  - Blood sample for future analysis (refer to Section 11.1.2.3).
- At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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

9.7.17. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (at selected study sites, where available) using the Fibroscan® TE device.
- Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.

- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.18. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject 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 and EOS procedures in the CRF.

Table 7: 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 IP	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[c]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[c]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

[a] Refer to Section 7.1.2 Schedule of Study Procedures, Table 2 for all procedures and evaluations required at the End of Treatment and End of Study Visits.

[b] Includes initiation of commercially available OCA.

[c] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE (where available) using the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).
- Conduct a DEXA bone density scan (selected study sites; not required at EOT/EOS if done within 6 months); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- 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 accountability, and review dosing diary with the subject; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19

- Markers of hepatic fibrosis and/or inflammation (including ELF)
- Blood sample for future analysis (refer to Section 11.1.2.3)

9.7.19. 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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin is observed during the course of the study, refer to Section 8.4.2.1 to confirm whether an unscheduled safety visit is required.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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

The 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 Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of 2 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Liver-related death
- Liver biochemistry (see Table 10 for list of analytes to be tested)
- Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) and ELF, Fibroscan (and others as determined during the course of the study).
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Non-Invasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF™ test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other Secondary Assessments

- OCA (OCA, tauro-OCA, glyco-OCA, total OCA, OCA glucuronide) and C4 will be assayed to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
- Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
- Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Appendix A 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 13.4) 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 13.4.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definition of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject 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.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.2. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 9, must be entered on the AE CRF. 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	Causing no limitation of usual activities; the subject may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the subject may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

12.1.4. Reporting of Adverse Events and Serious Adverse Events

12.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

12.1.4.2. 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 be reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521
- Telephone: +1 858 964 1571

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:

- Subject 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 investigational new drug (IND) 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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.

The Investigator is responsible for submitting information on IND 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND 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 12.1.5.

12.1.5. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.

For liver-related clinical outcome events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, please refer to Section 11.1.2.4.

The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), and spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).

12.1.6. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the medical monitor, 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 subject 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.

12.1.7. 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 SAE must be reported to the Sponsor immediately (ie, within 24 hours).

All SAEs that occur within 30 days following the cessation of investigational product, 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 12.1.4.2.

SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.

12.1.8. 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 subject 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 subject 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 CRF. 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.

12.1.9. 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 investigational product and the Sponsor must be notified within 24 hours of the Investigator's learning of the pregnancy by completing the Pregnancy Notification Form and faxing or emailing to the Sponsor at +1 800 497 8521 or sae@interceptpharma.com.

Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use of investigational product.

The subject may reinstate investigational product after delivery and cessation of breastfeeding (if applicable) at the discretion of the Investigator. Subjects whose pregnancy is terminated early

(planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see Section 8.4.1).

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening Visit 1, Month 12, and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Dual Emission X-Ray Absorptiometry

A bone density assessment will be done using the DEXA scan.

12.2.6. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.7. Laboratory Assessments

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

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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 10.

Table 10: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[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	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Measurement of Liver Fibrosis	Fibroscan
Bone Density Assessment	DEXA
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Blood Sample for Future Analysis	PBC autoantibodies and other cytokines and interleukins TBD
Other	OCA (parent and conjugates [glyco and tauro]) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.9 through pregnancy outcome.

MELD scores, Child-Pugh score, and MRS will be calculated at screening, and at quarterly (MELD and Child-Pugh scores) or semi-annual (MRS) visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Randomized Population will include all randomized subjects.
- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as

baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria where possible.

13.1.2. Determination of Sample Size

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.5 at 8 years with a hazard ratio of 0.60, and total study duration of 8 years, allowing for 2 years accrual and 6 years of follow up.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 121 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 350 subjects will be enrolled to attain 121 events.

13.1.2.1. Sample Size Re-Estimation Plan

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, starting approximately 2 years after the first subject is randomized, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 121 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.

Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities.

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.11 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the

OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3).

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time to event secondary efficacy analyses will compare randomized OCA versus randomized placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Analyses of changes in MELD score, Child-Pugh score, Mayo Risk Score (MRS), IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3× ULN and AST ≤2× ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5× ULN and AST ≤1.5× ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67× ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76× ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, “where no obvious single optimal external control exists, it may be advisable to study multiple external controls”. In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is “similar” to a participating subject. The historical database control

should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.3).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment.

Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a full range of covariates across which the treatment and historical controls might differ. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible.

Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation. Therefore, there is no chance of biasing results in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, hepatocellular carcinoma, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)

- Time to liver transplant or liver-related death
- Time to hepatocellular carcinoma

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.9. Alternative Primary Analysis

Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1). Similar statistical methodology as specified above in Section 13.1.8 for supportive analyses will be utilized.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

13.1.10. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

13.1.10.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.10.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.10.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified time point for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.11. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however, hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.12. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) based on the ITT population. Subgroups will be assessed at baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

13.2.4. Cardiovascular Adjudication Committee

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).

13.3. 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 subjects. 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 subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (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 subject safety, which alter the conduct of this study. The Investigators will inform the subjects of such actions and the protocol, patient information sheet (PIS), and consent will be revised, as appropriate.

13.4. Adjudication Committees

All suspected liver-related clinical outcomes, 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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject'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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. 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.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, medical monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 medical monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)

- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, 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 (when available) 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: The Sponsor, 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.

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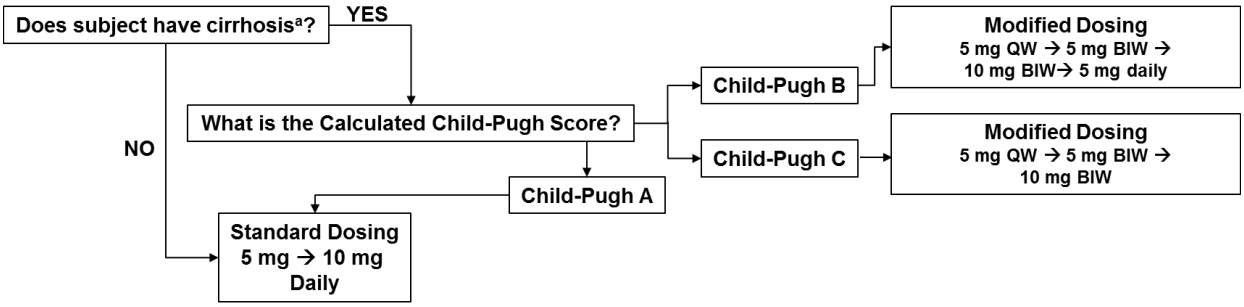
APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT

Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment

An overview of the modified dosing regimen for subjects with Child-Pugh Class B or Child-Pugh Class C is presented in Figure 2 and Table 11.

Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5 mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly.

Figure 2: Dosing by Cirrhosis Status and Child-Pugh Score



[a] Cirrhosis may be assessed by histology or non-histological methods as defined in Section 9.7.3.
BIW = twice weekly; QW = once weekly

Table 11: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Modified Dosing Regimen	
	Child-Pugh B	**Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg once weekly	5 mg once weekly
Titration 1 [b] (≥Month 3)	5 mg twice weekly[c]	5 mg twice weekly[c]
Titration 2 [b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]	10 mg twice weekly[c]
Titration 3 [b] (≥6 weeks after Titration 2)	5 mg daily	NA

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

Modified Dosing Regimen for Subjects with Child-Pugh B Hepatic Impairment

Subjects with cirrhosis and classified as Child-Pugh B at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in Figure 2. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and

following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to twice weekly dosing with 10 mg OCA or matching placebo. Subjects with at least 6 weeks of twice weekly dosing at 10 mg OCA or matching placebo, and meeting dose titration criteria, should up-titrate to the maximum allowed dose of 5 mg OCA or matching placebo once daily.

Investigators may decrease the dosing frequency (back to once or twice weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Modified Dosing Regimen for Subjects with Child-Pugh C Hepatic Impairment

Subjects with cirrhosis and classified as Child-Pugh C at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in Figure 2. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score

Subjects on a modified dosing regimen who demonstrate a change in cirrhosis status and/or Child-Pugh Score should have their dose of investigational product modified to match their current status per the appropriate dosing regimen (see Section 7.4, Table 5); however, changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as changes in status. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change to the dosing regimen. Investigators may contact the medical monitor at any time to discuss potential changes to dosing.

Possible scenarios for dosing modifications include:

- Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C
- Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study
- Improvement in classification of Child-Pugh Score from C to B
- Improvement in classification of Child-Pugh Score from B to A; these subjects may be eligible to transition to the standard dosing regimen

Subjects may titrate dose and dosing frequency up or down as appropriate, within the appropriate dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month Post-Titration

Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.10).

Unscheduled Titration Visit, Optional Visit

An unscheduled up-titration visit may be scheduled for as early as 6 weeks after the initial titration visit (or subsequent titration visit) occurs for subjects who are following the modified dosing regimen. The visit procedures required for the unscheduled titration visit are outlined below. Subjects who up titrate at an unscheduled visit will continue to follow the regular visit schedule for all other study visits.

For subjects who up titrate at an unscheduled visit the following procedures will be performed:

- Assess and record AEs.
- Review and record concomitant medications.
- Perform the pre-Titration Tolerability Assessment as outlined in Section 7.4.1.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

For subjects who up titrate at an unscheduled visit: The + 1-week window week related to the 1-Month Post-Titration visit can be extended for up to an additional 5 weeks to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the window is extended past +1 week allowed visit window, at a minimum, a telephone safety contact should then be performed 1-month post-titration.

APPENDIX B. LIST OF STUDY 747-302 OUTCOME EVENTS

Several of the specified clinical endpoints will also by definition (see Section 12.1) 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 12.1.4). 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

APPENDIX C. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

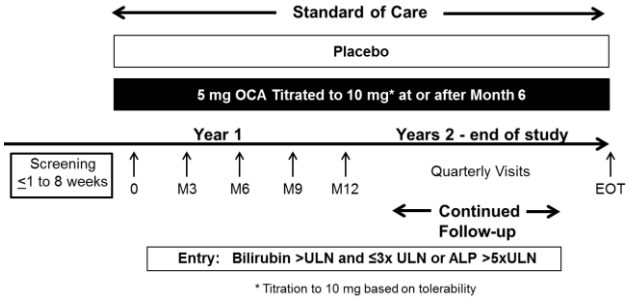
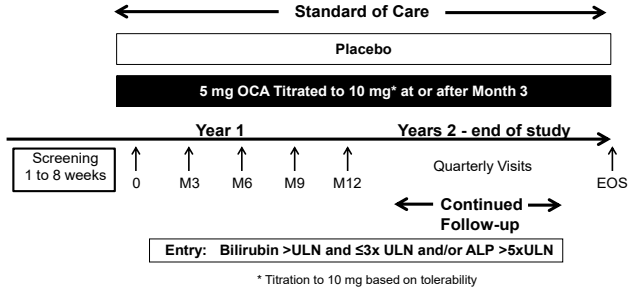
Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: xx April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact**:** PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD	Contact**:** PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2

Section	Original Text	Revised Text
	weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

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Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5×ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and/**or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12.	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>3. Mean total bilirubin >3× ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

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5. Deleted text</td></tr>
<tr><td>Synopsis</td><td><u>Criteria for Evaluation:</u><table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td><u>Criteria for Evaluation:</u><table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td><u>Statistical Methods: Other Efficacy Analyses</u>
• Added text</td><td><u>Statistical Methods: Other Efficacy Analyses</u>
• Development of varix/varices</td></tr>
<tr><td>4</td><td><u>List of Abbreviations</u>
Added text</td><td><u>List of Abbreviations</u><table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC.</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment.</td></tr>
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Section	Original Text	Revised Text
	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 **up to 4 years.** The **LSTE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete	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**.** The **LTSE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete
5.5.2.1	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.

Section	Original Text	Revised Text
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.**
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….

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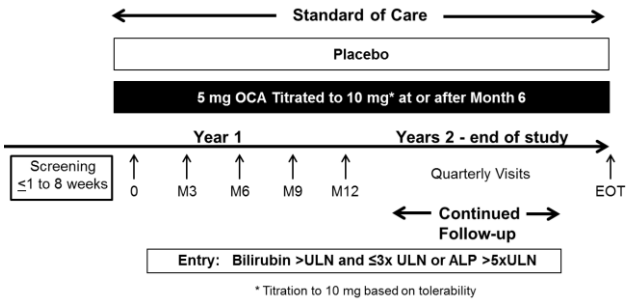
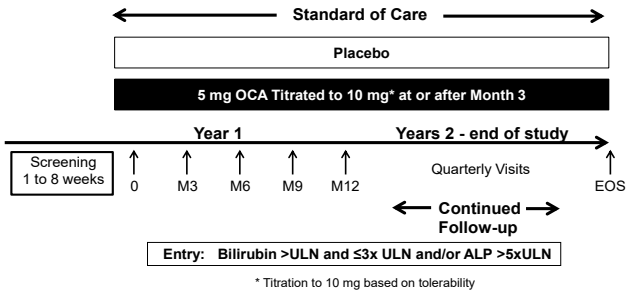
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)*** ***Visit Window ≤1 to 8 wks …*** ***Visit window in 2nd column added new text*** ***Added text*** *Footnote a:* All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on**	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now **"Screening Visit 1"*** *2nd column now **Screening Visit 2*** ***3** to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3*** *Footnote a* All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both**

Section	Original Text	Revised Text
	ALP (ALP >5× ULN), the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3× ULN).**	**analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**.
	Footnote b: The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed	*Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(± 1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.
	Footnote e: Medical history at Screening will smoking and alcohol consumption history and current habits for both.	*Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both.
	Footnote g: **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1)	*Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6)
	Footnote h: Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.	*Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote i: ***Added text***	*Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote j: ***Added text***	*Footnote j*: **Ultrasound will be conducted to enhance HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	*Footnote k***:** ***Added text***	*Footnote k:* **Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central**

Section	Original Text	Revised Text
		laboratory evaluations per the Child-Pugh scoring system noted in the case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
	Footnote l: ***Added text***	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
	Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change	***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***
7.3	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched

Section	Original Text	Revised Text
	placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5× ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and**/or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile),

Section	Original Text	Revised Text
	contraception during the study and for 30 days after the end of treatment visit.	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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** 4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3× ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**

Section	Original Text	Revised Text
	5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	**5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent. The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text***	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures)**. The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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 potential adjudicated hepatic and/or cardiovascular events**

Section	Original Text	Revised Text
	The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	Concomitant Medications 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 CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to**

Section	Original Text	Revised Text
		continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.
9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for**

Section	Original Text	Revised Text
		the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding. **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.**
9.6	Restrictions **No additional restrictions.**	Restrictions **Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment
</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
<tr><td>EOS
(When subject terminates the study)</td><td>The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject’s</td></tr>
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Section	Original Text	Revised Text
		participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study. EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**.	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart

Section	Original Text	Revised Text
	• For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).	• For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of **all available (at least 2; including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs**

Section	Original Text	Revised Text
		• **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours** – **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits** • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the**

Section	Original Text	Revised Text
		screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should**

Section	Original Text	Revised Text
		also be performed when platelet counts are <150 × 10^9 /L.
	• *Added text*	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• *Added text*	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• *Added text*	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**

Section	Original Text	Revised Text
9.7.6	Month 3 Procedures • ***Added text*** • ***Added text***	Month 3 Procedures • **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:** – **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • ***Added text***	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • ***Added text***	Month 9 Procedures • **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**

Section	Original Text	Revised Text
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.12), subjects who are participating in the PK assessment will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments**

Section	Original Text	Revised Text
		○ **Presence/absence of peripheral edema** ○ **Presence (degree)/absence of ascites** ○ **Presence (degree)/absence of hepatic encephalopathy**
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**

Section	Original Text	Revised Text
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1) • *Added text*	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will

Section	Original Text	Revised Text
		only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario**
		Table 7: Early Discontinuation Scenarios
		(Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
		[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7**.**
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.	Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing
	Prior to the EOT Visit:	Prior to the EOT/**EOS** Visit:
	During the EOT Visit:	During the EOT/**EOS** Visit
	• Subject questionnaires (see Section 12.2.6)	• Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)**
	• Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable	• Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
	• ***Added text***	• Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6)
	• ***Added text***	• Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months)
	• ***Added text***	• Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• *Added text*	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline**

Section	Original Text	Revised Text
		(and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of

Section	Original Text	Revised Text
	• ***Added text***	outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:** **a. PBC-40: The PBC-40 (Jacoby 2005) 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.** **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).**

Section	Original Text	Revised Text
		c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
12.1.1.2	Serious Adverse Event • ***Added text***	Serious Adverse Event **Events <u>not</u> 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**

Section	Original Text	Revised Text
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Section	Original Text	Revised Text
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to Appendix C)** and the Sponsor's policies.
19	List of References • Added text	List of References **Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83.** **Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.** **Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629.** **Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.**
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 (DATED 12 NOV 2015)

Rationale

The changes to Amendment 1 of the protocol, detailed below, generated specifically for regulatory authority requests, include an additional exclusion criteria and changes to text precluding UDCA naïve subjects from entering the study and clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, thus answering questions raised by regulatory authorities.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1.1. (Note: Revised text in Amendment 1.1 is indicated in bold font, and the text deleted from Protocol Amendment 1 is crossed out in the table below. Minor formatting changes are not listed.)

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
Title Page	Original: 03 October 2014 Amendment 1: 29 APRIL 2015	Original: 03 October 2014 Amendment 1: 29 **April** 2015 **Amendment 1.1: 12 November 201**
Study Personnel Contact Information	~~Mobile: PPD (Pacific time zone)~~ Telephone: PPD ~~Telephone~~ PPD	(deleted) Telephone: PPD (deleted)
Synopsis, Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
Synopsis, Statistical Methods: Sample Size Justification	• ~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)
8.3 Subject Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
9.2 Concomitant Medications	(insertion)	**The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile**

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
		of caffeine, a sensitive CYP1A2 substrate, 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.
12.1.4.2 Reporting of Serious Adverse Event	~~Mobile: PPD (Pacific time zone)~~ Telephone: +1 ~~858 964 1571~~	(deleted) Telephone: PPD
13.1.2 Determination of Sample Size	~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)

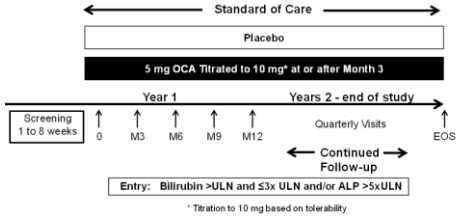
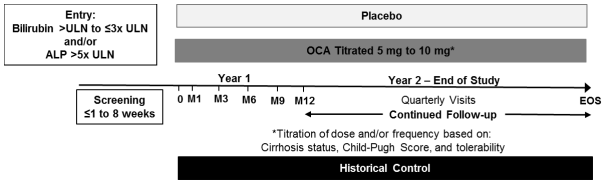
APPENDIX F. SUMMARY OF CHANGES: PROTOCOL VERSION 3 (DATED 07 SEPTEMBER 2016)

Rationale

The changes to Version 3 of the protocol, include dosing adjustments based on Child-Pugh scoring, additional exclusion criteria, changes to text precluding UDCA-naïve subjects from entering the study.

Please note that the Sponsor has renamed protocol "amendments" to "versions", therefore all future revisions that require a revised protocol will have an associated "version" number. The table below includes substantial revisions made to Protocol 747-302 under Version 3, which encompass the revisions captured in Protocol Amendment 1.1. Revised text in Version 3 is indicated in bold font, and the text deleted from Protocol Amendment 1.1 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 (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	... ~~Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups.~~ The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. ~~Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.~~	... Investigational product will be taken orally, once daily **for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C.** The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).	To incorporate a dosing and titration regimen based on subject's Child-Pugh Scores, to align with the recommended dosing regimen found in the Ocaliva US Package Insert for patients with hepatic impairment.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology. 7.1.1, Study Design Diagram, Figure 1	Schematic diagram 	Updated schematic diagram  **Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration**	Incorporate updated dosing scheme to reflect addition of Child-Pugh scoring.
Synopsis, Methodology	(insertion)	**Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:** • **Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.** • **For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.** • **Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or**	Revised methodology to incorporate the changes in dosing for subjects based on the Child-Pugh Scores.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. **Includes New Table: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	
5.1, Overview	(insertion)	**The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva™ for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication**.	Language updated as OCA is approved in the US with the trade name Ocaliva.
5.5.2.2, Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment	(Insertion)	**New section: Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment** **Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, no apparent impact on the overall safety profile was observed, consistent with**	Provide the rationale to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores into the protocol.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		only a modest increase in liver exposure of OCA associated with hepatic impairment. Collectively, the results from these analyses and those from bile acids in the literature suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure. **Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).**	
5.6, Summary of Known Potential Risks with OCA	(Insertion)	**…These findings were seen more frequently with doses above 10 mg OCA. In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.**	Added two AE terms reported in the updated Investigator's Brochure.
7.1, Overall Study Design	…~~Investigational product will be initiated at 5 mg OCA or matched placebo.~~ Following 3 months of treatment with investigational product, ~~subjects~~ should be titrated ~~in a blinded manner (ie, subjects randomized to OCA will increase their dose to~~ 10 mg OCA) based on tolerability	Investigational product will be taken orally, once daily**. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo.** Following 3 months of **once daily** treatment with investigational product, **the dose** should be titrated **to a maximum** 10 mg OCA **or matching placebo once daily**, based on tolerability (see Section 7.3). **Subjects with cirrhosis and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.**	Amend the protocol to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.1.2, Table 1, Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2), 9.3, Treatment compliance	~~Safety Contact~~	This visit has been deleted.	Replaced with the 1 Month Post-Titration Visit.
	(Insertion)	Added the following visits: • Month 1 • 1 Month Post-Titration Visit	Visits were added to accommodate the updated dosing and titration regimen based on subject's Child-Pugh Scores.
	~~[b]The subject should be contacted by telephone on a monthly basis in between at clinic study visits at Month 1 and Month 2 (± 1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.~~ ~~[e]As soon as possible upon study discontinuation and as near as possible to last dose taken.~~ ~~[n]Subject to begin dosing on Day 1~~	Deleted.	Result of table being updated for the dosing and titration regimen based on subject's Child-Pugh Scores.
	(Insertion)	Added the following study procedures: • Cirrhosis Status Assessment[e] • Assessments for Child-Pugh Scores[g] • Dose Titration: Standard Dosing[n,o] • Dose Titration: Modified Dosing [n,o] • Dosing Diary	Study procedures were added to accommodate the updated dosing/titration regimen. Dosing diary was added to improve compliance.
	(Insertion)	Added the following footnotes: • [b]Safety Post-Titration visits must be performed 1 month + 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after	Added footnotes provide clarity regarding assessments and visits based on the evaluation of Child-Pugh scores.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency. • [e]Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated. • [f]Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF. • [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. • [n]Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment. • [o]Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh score (Section 7.3). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A. • [p]Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately	

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.	
7.1.2, Table 2, Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)		**New table- Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)**	Divided Schedule of Study Procedures into 2 tables, updated to include visits added per updated dosing/titration information.
7.3, Planned Dosing Regimen	7.3 ~~Treatment Assignment~~ ~~Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3-month study visit or at any study visit thereafter depending on tolerability.~~	**7.3 Planned Dosing Regimen** Subjects will **be randomized to treatment with** either **OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.** **Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).** **For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to**	Section renamed to reflect changes in titration and dosing for subjects with hepatic impairment.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.	
	(Insertion)	**New: Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Tables added to clarify changes in titration and dosing.
		New: Table 4: Determination of Dosing Regimen	
7.4 Dose Titration Criteria	~~After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA~~ or ~~matched placebo (in a blinded manner) at the 3 month visit or any study visit following the 3 month visit based on~~ tolerability ~~of investigational product~~. ~~For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10 mg dose if tolerated~~	**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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh Score.** **Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.** **Tolerability Dose Titration - Investigators** may decrease **the dosing frequency** or dose **for any subject** at any time during the study, as considered **clinically** appropriate (eg, tolerability; **see Section 7.4.2).** **Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due** to **changes in cirrhosis or Child-**	Entire section revised to reflect changes in titration and dosing.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		Pugh 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.	
7.4 Dose Titration Criteria	(Insertion)	**New: Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score**	Section and table added to provide dosing guidelines to investigators.
7.4 Dose Titration Criteria	(Insertion)	**Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).** **Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).** **Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.** **Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in**	

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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. **Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.**	
7.4.1, Pre-Titration Tolerability Assessment Requirements	(Insertion)	**7.4.1 Pre-Titration Assessment Requirements** **Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in study medication (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.** **To be eligible for a dose up-titration:** **• Subjects should not be experiencing significant AEs that are suspected to be related to investigational**	Section added to provide guidance for assessing subject tolerability prior to titration.

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		product (eg, severe pruritus) or displaying other symptoms that may indicate intolerability of investigational product. • **There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required**	
8.4.2, Other Reasons for Discontinuation of Study or Investigational Product	(Insertion)	• **Subject begins treatment with commercially available OCA** **… safety concerns and related to study drug** • Consent may be fully withdrawn **(in which case the subject discontinues both investigational product and study visits and procedures)** **…Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.**	Added text as Ocaliva is commercially available in the US and therefore subjects may be discontinued if they began off-study treatment with Ocaliva.
8.4.2.1, Elevated Liver Enzymes	(Insertion)	**New Section: 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**	Section added to incorporate monitoring of liver test results during the study.

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		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.**	
9.1, Investigational Product Treatment Regimen	~~**9.1.1 Dose Adjustment Beginning at Month 3**~~ ~~After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted~~.	**At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.**	Section revised to reflect changes in titration and dosing.
9.2, Concomitant Medications	Subjects taking bile acid sequestrants (BAS) 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).	New sub-heading**:** ***Drug Interactions*** Subjects 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 INR levels, therefore, INR should be monitored and the dosage of warfarin adjusted, as**	Section revised to provide additional information on drug-drug interactions with OCA.

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		needed during treatment with OCA and after cessation of OCA, to maintain the target INR range. (…) **Information related to additional drug-drug interaction (DDI) studies is available in the current version of the Investigator's Brochure (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 with OCA that may be observed in study subjects.**	
9.2.1, Prohibited Medications	… the Investigator should be cognizant of the possibility of double dosing ~~and encourage the discontinuation of open-label OCA therapy. However, if~~ commercial OCA therapy ~~remains, then investigational product should be discontinued to avoid potential double dosing~~. ~~Subjects that discontinue investigational product but continue commercial OCA therapy~~ are expected to continue through the end of the study, ~~and~~ the …	… the Investigator should be cognizant of the possibility of double dosing. **Subjects who continue with** commercial OCA therapy **must** discontinue **study medication and** are expected to continue through the end of the study. …	Ocaliva is commercially available in the US and, therefore, subjects wishing to take commercially available drug are not discouraged, but they must discontinue study medication.
9.7.1, Visit Windows	(insertion)	**Added the following visit windows:** • **Month 1 (+1 week [7 days])** • **Titration Visit – Standard Dosing Regimen (≥Month 3)** • **Titration Visit 1 – Modified Dosing Regimen (≥Month 3)** • **Titration Visit 2 – Modified Dosing Regimen (≥6 weeks after Titration Visit 1)** • **Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY) (≥6 weeks after Titration Visit 2)** • **Post-Titration Visit, (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency)**	Added visits to accommodate the updated dosing/titration scheme.

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9.7.3, Assessing Cirrhosis	(Insertion)	**New: 9.7.3. Assessing Cirrhosis** **To determine which dosing regimen subjects should follow, the presence or absence of 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 is defined as a subject 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/mm3) with:** **– persistent decrease in serum albumin, or** **– elevation in prothrombin time /INR (not due to antithrombotic agent use), or** **– elevated bilirubin (2× ULN)** **Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A).**	Added section to assess cirrhosis as this assessment will determine the acceptable dosing regimen based on a subject's Child-Pugh score.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		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, Child-Pugh Score	(Insertion)	**9.7.4. Child-Pugh Score** **Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh 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.** **It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen**	Section added to provide Investigators with information on the Child-Pugh scoring system.
9.7.4, Child-Pugh Score	(Insertion)	**Table 6 (New) Child-Pugh Scoring System**	
9.7.6, Screening Procedures (1 to 8	(Insertion)	The following procedures were added: Screening Visit 1 procedures are as follows: • **Provide the subject with a dosing diary to**	Procedures added to assess cirrhosis.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Weeks prior to Day 0)		**document his or her dosing** • **Assess for the presence/absence of cirrhosis** • **Perform status assessment for calculation of Mayo Risk Score** Screening Visit 2 procedures are as follows: • **Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.**	
9.7.7, Day 0 Procedures (Randomization)	9.7.4. ~~Day 0 Procedures~~ ~~• Perform an ultrasound for hepatocellular carcinoma (HCC) surveillance (if equipment is unavailable, …~~ ~~• Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.~~ ~~□ Presence/absence of peripheral edema~~ ~~□ Presence (degree)/absence of ascites~~ ~~□ Presence (degree)/absence of hepatic encephalopathy~~	9.7.**7**: Day 0 Procedures (Randomization) • **Provide the subject with a dosing diary to document his or her dosing.**	Updated visit to accommodate the updated dosing/titration scheme.

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9.7.8, Month 1 Procedures	9.7.5 Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone])	9.7.**8** Month 1 Procedures • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:** - **At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, …** - **If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. …**	Revised section to include the new Month 1 visit procedures.
9.7.9, Month 3 procedures, 9.7.11, Month 6 Procedures, 9.7.12, Month 9, 9.7.14, Month 12 Procedures	(Insertion)	• **Perform assessments for calculation of Child-Pugh Score**	Added procedure to accommodate the updated dosing/titration scheme.
9.7.9 thru 9.7.17	(Insertion)	**If up titration will occur at this visit, complete the pre-titration visit and visit related assessments as outlined to ensure all procedures required for dose titration eligibility have been met, including the required review of the dose titration laboratory parameters.** • **Provide the subject with a dosing diary to document his or her dosing**	Text added to clarify procedures required before up-titration.

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		• **… review dosing diary with the subject**	
9.7.10, Post Titration Visit Procedures	(Insertion)	New**: 9.7.10. Post Titration Visit Procedures** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.** • **Obtain blood samples for serum chemistry, hematology, and coagulation tests.** • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration visit requirements:** **- At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.** **- If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be**	Added visit to accommodate the updated dosing/titration scheme.

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		provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance. • **Schedule the next visit, reiterate dosing instructions, and advise the subject:** **- 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…**	
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	(Insertion)	**…Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule**.	Clarify that subjects with hepatic impairment may continue to participate in the PK assessment.
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink…	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink **with no other food allowed until after the final 6-hour post dose sample is collected…**	Clarify PK collection procedures.
11.1.2.2, Other Secondary Assessments	• OCA (~~and its conjugates~~) and C4 will be assayed	• OCA **(OCA, tauro-OCA, glyco-OCA, total OCA, OCA glucuronide)** and C4 will be assayed **to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified**.	Clarify the analytes to be measured for the PK analyses.

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11.1.2.4, Potential Clinical Outcome Events	(Insertion)	**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 13.4.**	Revised to clarify that potential clinical outcome events meeting the criteria of a SUSAR will not be reported to regulatory authorities expeditiously.
12.1.4.2 Reporting of Serious Adverse Event	In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the ~~medical monitor.~~ All SAEs ~~occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious)~~ must be reported to the ~~medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE~~. SAEs are reported by entering the SAE data into the ~~electronic data capture (EDC) system~~. Entering the SAE data into the EDC system will automatically notify the ~~medical monitor~~ of the event. In the event that the EDC system is inaccessible, an SAE may be reported by ~~telephone or fax~~ using a paper SAE Report form. 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	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 be reported by: • **E-mail to the SAE email address: sae@interceptpharma.com** • **Fax** using a paper SAE **report** form: **+1 800 497 8521** • **Telephone: +1 858 964 1571** 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: • **Subject** number	Updated guidance for reporting SAEs.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	information should be provided at the time of the initial report: ~~subject~~ number and ~~initials, a description of the event~~, at least **one** criterion classifying the event as serious and the name and title of the reporting individual. ~~Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting~~ to regulatory authorities by the Sponsor or designee(s). ~~Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible~~. 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. ~~A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).~~ The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) ~~safety reports (SUSARs)~~ that occur during the study within the time frames required by	• **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 Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) **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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.** **The Investigator is responsible for submitting information on IND 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND 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 12.1.5.**	

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	each regulatory agency. ~~The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).~~ ~~Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities~~		
Section 12.1.5, Suspected Liver-related Clinical Outcome Events	Clinical Outcome Events ~~(Appendix A) as well as Anticipated Events (Appendix B) will not undergo~~ expeditous reporting.	**12.1.5 Suspected Liver-Related Clinical Outcome Events** **Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.** **Given that the liver-related clinical outcome events could also meet the criteria of a SUSAR, please refer to Section 11.1.2.4.** **The Sponsor will consider the following list of clinical outcome events (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**	Updated section to account for events related to hepatic impairment**.**

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		haemorrhage), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial and peritonitis (preferred term: peritonitis bacterial).	
13.2.4, Cardiovascular Adjudication Committee	13.2.3 (…) In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study ~~and will be described separately~~.	**New Section: Cardiovascular Adjudication Committee** In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. **Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).**	Committee added to assess cardiovascular events in subjects during the study.
13.4, Adjudication Committee	All ~~potential endpoint events~~ will be reviewed by ~~an~~ adjudication committee before inclusion in the any analysis. The ~~adjudication of potential clinical endpoint~~ events will include, ~~but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential~~	All **suspected liver-related clinical outcomes, 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**	Committee S added to assess liver impairment in subjects during the study.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	~~documents. A separate adjudication committee charter will document the entire data flow and process from committee membership~~, the reporting of events by the study site, ~~reporting~~ of the ~~final assessment,~~ supply of source documentation to the committee, ~~the~~ review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members ~~will remain blinded to treatment group throughout the study~~. ~~In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.~~	• **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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.**	
Appendix A, Modified Dosing Regimen for Subjects with Child-Pugh B/C	(Insertion)	New**: APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT**	Added section to describe changes in dosing and titration for subjects assessed as cirrhotic Child-Pugh B or Child-Pugh C.

Section	Original Text (Amendment 1.1, 29 April 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Hepatic Impairment			
Appendix B, LIST OF STUDY 747-302 OUTCOME EVENTS	Was Appendix A	Now Appendix B	The hepatic dosing appendix became Appendix A
Appendix C	~~LIST OF STUDY 747-302 ANTICIPATED EVENTS~~	Deleted	Replaced by Appendix A, more comprehensive description of the outcome events.

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Version 3.1: 21 December 2016

(For FDA Review Only)

Sponsor

Intercept Pharmaceuticals, Inc.
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TEL: +1 858 250 6398

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD , PhD

12/21/16

Date

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigational Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-302. 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor – 24-hour Emergency Reporting

Contact:	PPD MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.
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Email:	PPD
SAE Fax:	+1 800 497 8521
SAE Email:	sae@interceptpharma.com

Or if Not Available:

Contact:	PPD MD, PhD Medical Director, Clinical Research, Intercept Pharmaceuticals, Inc.
Telephone:	PPD
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Clinical Operations and Project Management

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid (OCA)

Name of Active Ingredient:

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

Title of Study:

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

Investigators and/or Study Center(s):

Approximately 170 investigational study sites, globally.

Studied Period (years):	**Phase of Development:**
The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Phase 4

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cirrhosis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above

To assess the effect of OCA compared to placebo on time to first occurrence of liver related death.

To assess the effect of OCA compared to placebo on progression to cirrhosis To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To characterize the pharmacokinetics of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

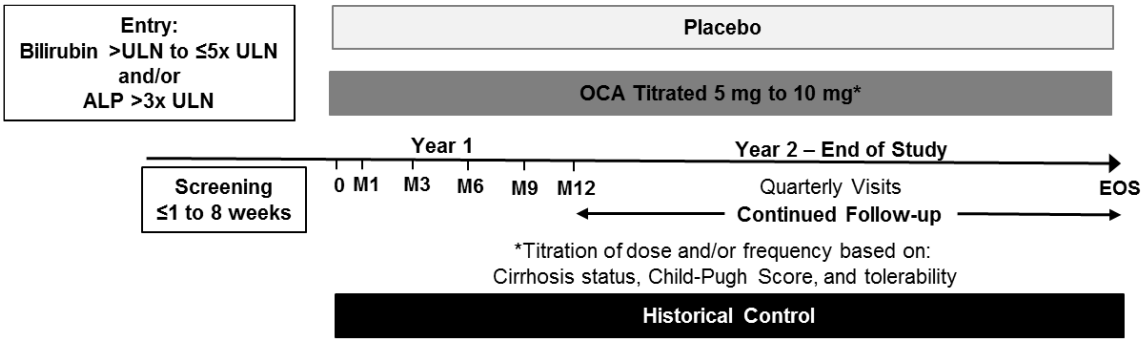
To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened twice during a 1 to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.6).

Investigational product will be taken orally, once daily for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (> upper limit of normal [ULN]/ ≤ ULN).

Schematic Diagram:



EOS = end of study; ULN = upper limit of normal
Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:

- Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.
- For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.
- Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability and biochemical response. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability and biochemical response.

Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Planned Dosing Regimen		
	Standard	Modified	
	Non-Cirrhotic/ Child-Pugh A	Child-Pugh B	Child-Pugh C
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly	5 mg twice weekly
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly	10 mg twice weekly
Titration 3 [b] (≥6 weeks after Titration 2)	NA	5 mg daily	NA

[a] Starting dose based on subject's cirrhosis status and Child-Pugh Score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.

Number of Subjects (planned):

Approximately 428 subjects

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤5× ULN and/or a mean ALP >3× ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
   - Intrauterine device (IUD)
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence, if in line with the preferred and usual lifestyle of the subject
6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection

- Active hepatitis B infection; however, subjects 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
- Nonalcoholic steatohepatitis
- Gilbert's Syndrome

2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy
     – Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)
3. Mean total bilirubin >5× ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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-month 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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
14. UDCA naïve (unless contraindicated)

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Reference Therapy, Dosage and Mode of Administration:

Placebo (matching tablets)

Duration of Treatment:

It is expected that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 127 total primary endpoint events.

Criteria for Evaluation:

Primary Objectives	**Assessments**
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Progression to cirrhosis	Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated
Change in baseline liver biochemistry	Liver biochemistry (see Table 10) for list of analytes to be tested
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhanced liver fibrosis (ELF), and Fibroscan® TE
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
Pharmacokinetics	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events Clinical laboratory values

Statistical Methods:

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBC Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Efficacy Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy

All events will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 its 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory.

Other Efficacy Analyses

The following secondary efficacy analyses will compare OCA to placebo on time to the following events:

- Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above)
- Development of varix/varices

- Liver-related death
- Liver-related death or liver transplant
- Liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Progression to cirrhosis will be assessed in the subset of subjects considered non-cirrhotic at baseline using available medical history, clinical, and laboratory assessments as well as baseline transient elastography (TE) where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered non-cirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the trial in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of non-cirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.

Analyses for the histological assessment conducted as part of the biopsy sub-study are defined in Appendix C.

Further details on efficacy, health outcomes, and pharmacokinetic analyses are specified in Section 13.

Safety Analyses

Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will be summarized by treatment group for the Safety Population.

Sample Size Justification

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years subject accrual and 6 years of follow-up
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance
- Two interim analyses and one final analysis are planned

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
CAC	Cardiovascular Adjudication Committee
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DEXA	dual-emission X-ray absorptiometry
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
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FIS	Fatigue Impact Scale
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid

Abbreviation or Specialist Term	Explanation
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
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
LDL	low-density lipoprotein
LTSE	long-term safety extension
MACE	major adverse cardiovascular events
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PSC	primary sclerosing cholangitis
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
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.

Abbreviation or Specialist Term	Explanation
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 Primary Biliary Cirrhosis and Obeticholic Acid

Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis) 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, is currently the only treatment approved for PBC (Lindor 2009). While UDCA therapy has a marked effect on the treatment of PBC, up to 50% of patients show a suboptimal response or no response to UDCA. Such patients are at significantly increased risk of a poor clinical outcome due to PBC disease progression. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]). Obeticholic acid (OCA) is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary human bile acid chenodeoxycholic acid (CDCA). OCA is currently being developed in the United States (US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication.

5.2. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 31 Jan 2016, approximately 1726 subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 458 subjects had PBC, 330 subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease (NAFLD), 33 subjects had alcoholic cirrhosis/portal hypertension, and 20 subjects 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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects reaching specific criteria for ALP and bilirubin (ALP $<1.67\times$ upper limit of normal [ULN] with a $\geq 15\%$ reduction and bilirubin $\leq$ULN). Both OCA treatment groups met the primary endpoint of achieving a

reduction in ALP to <1.67× 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 10 mg OCA 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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rationale for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. As a result, starting subjects on 5 mg OCA and titrating to 10 mg based on tolerability and clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Dose

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Based on these data, the indicated commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.

5.5.2.2. Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh Score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).

5.5.2.3. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Summary of Known Potential Risks with OCA

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, but with a much lower frequency than that observed in subjects with PBC.

An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg and in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies.

In subjects 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 above 10 mg OCA. 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 (HDL) and an increase in low density lipoprotein (LDL). Notably, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.

Refer to the IB for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above and also to include liver-related death.

To characterize the effect of OCA compared to placebo on progression to cirrhosis.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To assess the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 4, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤5× ULN and/or ALP >3× ULN. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 428 subjects meeting all enrollment criteria will be recruited into the study over an approximate 4-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). Subjects will be screened during a 1 to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.6). Randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used.

Subjects will be dosed according to their cirrhosis status and Child-Pugh Score. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo. Following 3 months of once daily treatment with investigational product, the dose should be titrated to a maximum 10 mg OCA or matching placebo once daily, based on tolerability and biochemical response (see Section 7.3).

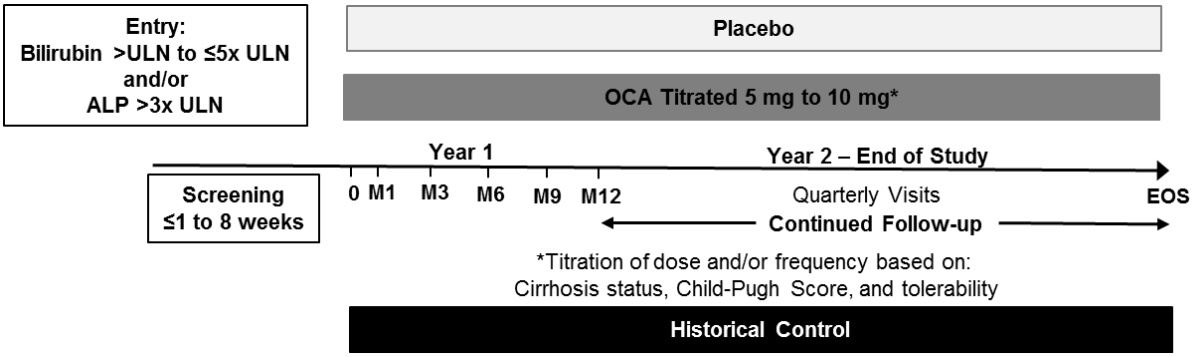
Subjects with cirrhosis (see Section 9.7.3) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.

It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 127 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.

This study will be conducted at approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; ULN = upper limit of normal
Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2)

	Screening Visits		Day 0	M 1	M 3	1-Month Post-Titration Visit[b]	M 6	M 9	M 12
	1	2[a]							
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Informed Consent	X								
Medical/PBC History[d]	X								
Cirrhosis Status Assessment[e]	X								
Inclusion/Exclusion Criteria	X	X	X						
Physical Exam	X			X		X	X		X[d]
Assessments for Mayo Risk Score[f]	X						X		X
Assessments for Child-Pugh Score[g]	X				X		X	X	X
Vital Signs (including weight)	X[h]		X		X		X	X	X[h]
12-Lead Electrocardiogram	X								X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X				X		X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[i]			X						X
Fibroscan® TE[j]			X				X		X
DEXA[k]			X						X
Endoscopy[l]			X						X
Hepatic Ultrasound[m]		X					X		X
Adverse Events	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Health Outcome Assessments[n]			X		X		X	X	X

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2) (Continued)

	Screening Visits		Day 0	M 1	M 3	1-Month Post-Titration Visit[b]	M 6	M 9	M 12
	1	2[a]							
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Randomization/Treatment Assigned			X						
Dose Titration: Standard Dosing[o,p]					X		X (if applicable)		
Dose Titration: Modified Dosing (if applicable)[o,p]					X		X	X	X
Dispense Investigational Product[q]			X		X		X	X	X
IP Accountability/Compliance				X	X	X	X	X	X
Dosing Diary			X	X	X	X	X	X	X
LABORATORY EVALUATIONS[r]									
Urinalysis	X		X						X
Urine-based β-hCG Pregnancy Test[s]	X		X						
Chemistry/Hematology/Coagulation	X	X[a]	X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X		X		X	X[t]	X
Markers of Hepatic Fibrosis and/or Inflammation[u]			X				X		X
Genetics[v]			X						X
Blood Sample for Future Analysis[w]			X				X		X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] Post-Titration visits must be performed 1 month (+ 1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.
[e] Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.
[f] Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the eCRF.
[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] Height will be collected at this visit.
[i] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).
[j] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.
[k] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.
[l] Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed window at Day 0 for this specific procedure.
[m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: unless HCC has already confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.
[n] Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.
[o] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.
[p] Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh Score (Section 9.7.4). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.
[q] Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.
[r] The subject 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.
[s] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at the central laboratory. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
[t] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.13 for the PK sampling schedule.
[u] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.
[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. If a baseline (e.g. Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.
[w] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2)

	Year 2 through End of Study					
	M 3 continued follow-up	**1-Month Post-Titration Visit[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**+1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Physical Exam[d]		X			X	X
Assessment for Mayo Risk Score[e]			X		X	X
Assessments for Child-Pugh Scores[f]	X		X	X	X	X
Vital Signs (including weight)			X		X[g]	X[g]
12-Lead Electrocardiogram					X	X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[h]					X	X
Fibroscan®TE[i]			X		X	X
DEXA[j]					X	X
Endoscopy[k]					X	
Hepatic Ultrasound[l]			X		X	X
Adverse Events	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Health Outcome Assessments[m]	X		X	X	X	X
Dose Titration (if applicable)[n,o]	X		X	X	X	
Dispense Investigational Product	X		X	X	X	
IP Accountability/Compliance	X	X	X	X	X	X
Dosing Diary	X	X	X	X	X	X
LABORATORY EVALUATIONS[p]						
Urinalysis					X	X
Chemistry/Hematology/Coagulation	X	X	X	X	X	X

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2) (Continued)

	Year 2 through End of Study					
OCA, C4, and FGF-19 (plasma)					X	X
Markers of Hepatic Fibrosis and/or Inflammation[q]			X		X	X
Genetics[r]					X	
Blood Sample for Future Analysis[s]			X		X	X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency. Post-titration visits must be performed 1 month ± 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment.

[b] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] The yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.

[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 case report form.

[g] Height will be collected at this visit.

[h] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).

[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. Not required if done within 3 months of visit

[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Not required if done within 6 months of visit.

[k] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices.

[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.

[m] Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[n] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[o] Dose Titration is based on cirrhosis status (see Section 9.7.3) and Child-Pugh Score (Section 9.7.4). The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

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

[q] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[r] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.

[s] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 428 subjects will be randomized in the study to achieve 127 adjudicated primary endpoint events.

7.3. Planned Dosing Regimen

Subjects will be randomized to treatment with either OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.

Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5 mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product and assessment of biochemical response. Up-titration should be considered when ALP and/or total bilirubin are >ULN. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).

For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.

Table 3: Planned Dosing Regimen by Cirrhosis and Child Pugh Score

	Scheduled Dosing Regimen		
	Standard	**Modified**[a]	
	Non-Cirrhotic/ Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Starting Dose[b] (Day 0)	5 mg daily	5 mg once weekly	5 mg once weekly
Titration 1[c] (≥Month 3)	10 mg daily	5 mg twice weekly[d]	5 mg twice weekly[d]
Titration 2[c] (≥6 weeks after Titration 1)	NA	10 mg twice weekly[d]	10 mg twice weekly[d]
Titration 3[c] (≥6 weeks after Titration 2)	NA	5 mg daily	NA

[a] Refer to Appendix A for additional instructions regarding subjects following the Modified Dosing Regimen.
[b] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening.
[c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4).
[d] Dosing per the twice weekly schedule must be at least 3 days apart.

The dosing regimen should be determined as described in Table 4. Investigators should follow the dosing/titration schedule as shown in Table 3.

Table 4: Determination of Dosing Regimen

Cirrhosis?	No	Yes	Yes	Yes
Child-Pugh Score	Any	A	B	C
Dosing Regimen	Standard		Modified for Child-Pugh B	Modified for Child-Pugh C

7.4. Dose Titration 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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh 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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.

Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability; see Section 7.4.1 and Section 7.4.2).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due to changes in cirrhosis or Child-Pugh 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.

Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score

Original Status	**New Status**[a]		
	Non-cirrhotic *OR* Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Non-cirrhotic *or* Child-Pugh A	*No Change*	10 mg daily → 5 mg daily 5 mg daily →No change **or** 10 mg twice weekly[b]	5 mg or 10 mg daily → 10 mg twice weekly[b]
Child-Pugh B	5 mg daily → 10 mg daily	*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	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 subject begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.3 or Appendix A.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the Investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).

Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).

Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.

Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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.

Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in study medication (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.

To be eligible for a dose up-titration:

- Subjects 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.
- There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required.

7.4.2. Safety Criteria for Adjustment or Stopping Doses

Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.

7.5. Criteria for Study Termination

The Sponsor 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 DMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 127 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.

2. A mean total bilirubin >ULN and ≤5× ULN and/or a mean ALP >3× ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects of child-bearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
   - Intrauterine device (IUD)
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence, if in line with the preferred and usual lifestyle of the subject
6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.

- Cirrhosis with complications, including history (within the past 12 months) or presence of:
  - Variceal bleed
  - Uncontrolled ascites
  - Encephalopathy
  - Spontaneous bacterial peritonitis
- Known or suspected hepatocellular carcinoma
- Prior transjugular intrahepatic portosystemic shunt procedure
- Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)

3. Mean total bilirubin >5× ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
14. UDCA naïve (unless contraindicated)

8.4. Subject Withdrawal from Investigational Product or Study

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

8.4.1.1. Severe Drug-Induced Liver Injury

If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. Subjects who develop significant drug-induced liver injury which is considered 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, evidence of 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.

Severe drug-induced liver injury that is not considered related to investigational product must be discussed with the Sponsor before investigational product is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time.

All suspected drug-related hepatic injury events will be adjudicated by the Hepatic Safety Committee (see Section 13.4).

8.4.1.2. Liver Transplantation

Subjects must discontinue investigational product after undergoing liver transplantation surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection.

8.4.2. Reasons for Mandatory Interruption of Investigational Product

Prior to re-starting investigational product after a prolonged interruption, the subject must be re-consented and new baseline visit procedures must be performed if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.

8.4.2.1. Pregnancy

If a female subject becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 12.1.9 pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 12.1.9). New baseline procedures should include pregnancy testing.

8.4.3. Other Reasons for Discontinuation of Study or Investigational Product

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. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18).

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

- Subject begins treatment with commercially available OCA
- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- 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 subject 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), liver-related clinical outcomes, and drug-related hepatic injury events.

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

8.4.3.1. 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.

8.4.4. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.5. Lost to Follow-Up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.6. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.18, Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or matching 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 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, up to once daily, for the duration of the study.

All subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Drug Interactions

Subjects 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 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 Investigator's Brochure (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 with OCA that may be observed in study subjects.

PBC-Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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. Subjects who continue with commercial OCA therapy must discontinue study medication and are expected to continue through the end of the study (see Section 7.4.2). The study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (see Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).

9.3. Treatment Compliance

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

Subjects should be instructed to complete a dosing diary to help monitor compliance to the prescribed dosing regimen. Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable, follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to one of two treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2 below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects 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 subject). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the subject'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 subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The Data Monitoring Committee (DMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded subject data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the trial 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 Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0. The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening Visit 1 interval is 3 to 8 weeks prior to Day 0. Screening Visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Month 1	+1 week (7 days)
Titration Visit – Standard Dosing Regimen	≥Month 3
Titration Visit 1 – Modified Dosing Regimen	≥Month 3
Titration Visit 2 – Modified Dosing Regimen	≥6 weeks after Titration Visit 1
Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY)	≥6 weeks after Titration Visit 2
Post-Titration Visit	1 month (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency
Month 3 to Month 12	±2 weeks (14 days)
Quarterly visits (Months 15 to EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study.

EOS = end of study; EOT = end of treatment

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Assessing Cirrhosis

9.7.3.1. Determination for Dosing Regimen

To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of determining dosing is defined as a subject 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 (TE) 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)

Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A, Section 7.3, Table 3 and Table 4).

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

9.7.3.2. Progression to Cirrhosis

When a subject identified as non-cirrhotic at baseline per the criteria listed in Section 9.7.3.1 exhibits any of those same criteria (excluding biopsy results consistent with PBC Stage 4), the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites participating in the paired biopsy sub-study (see Appendix C) must confirm progression to cirrhosis by biopsy. All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.

9.7.4. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh 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. It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen.

Table 6: 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)

9.7.5. Mayo Risk Score

Mayo Risk Score (MRS) (Dickson 1989) is calculated and reported within the EDC system based on data entered into the eCRF. Calculation of MRS includes investigator assessment of peripheral edema and the use of diuretic therapy, which will be assessed during adverse event and concomitant medicine review at the scheduled visits and entered into the eCRF, as well as total bilirubin, albumin, and prothrombin time results obtained from the central laboratory data.

9.7.6. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 week to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 3 weeks to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 week to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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.

Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤5× ULN and/or an ALP >3× ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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
- Assess for the presence/absence of cirrhosis.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score
- Perform assessment for calculation of Mayo Risk Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).

- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.
- Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.
- Assess and record any pretreatment-emergent AEs.
- Record current concomitant medications.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.
- In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate.

9.7.7. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform transient elastography at all study sites with access to Fibroscan® TE device. If TE has been done within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc), the procedure may be completed within the screening visit window, at Screening Visit 1 (if data is needed for cirrhosis assessment) or as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
- Conduct a DEXA bone density scan (at all study sites where device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
- Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where device is available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
  - Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- 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 subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.

  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- 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 tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF])
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Access the IWRS and dispense investigational product
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 1 Procedures

- Perform a physical examination.
- Assess and record AEs
- Review and record concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.

- In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit laboratory requirements:
  - At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Month 1 visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Month 1 visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- 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.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF

  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Post-Titration Visit Procedures

- Perform a physical examination.
- Assess and record AEs.
- Review and record concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration laboratory requirements:
  - At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A

copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 6 Procedures

- Perform a physical examination
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Perform TE at all study sites with access to Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.12. Month 9 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- 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.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- PK assessment in participating subjects at select study sites (see Section 9.7.13).
- In preparation for the DEXA bone density scan to be done at the Month 12 visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.13. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule.

Following collection of the Month 9 fasted samples (refer to Section 9.7.12, subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of study medication and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the study medication (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4-hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink with no other food allowed until after the final 6-hour post-dose sample is collected. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.14. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires and (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE at all study sites with access to Fibroscan® TE device.
- Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.

- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.15. Month 3 and Month 9 Continued Follow-Up Procedures (±2 weeks)

- Perform assessments for calculation of Child-Pugh Score.
- Assess and record AEs.
- Review and record concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.16. Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])

- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Perform TE at all study sites with access to Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
  - Blood sample for future analysis (refer to Section 11.1.2.3).
- At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is

taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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

9.7.17. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE at all study sites with access to Fibroscan® TE device.
- Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.

- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.18. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject 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 and EOS procedures in the CRF.

Table 7: 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 IP	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[c]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[c]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

[a] Refer to Section 7.1.2 Schedule of Study Procedures, Table 2 for all procedures and evaluations required at the End of Treatment and End of Study Visits.

[b] Includes initiation of commercially available OCA.

[c] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE at all study sites with access to the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).
- Conduct a DEXA bone density scan (selected study sites; not required at EOT/EOS if done within 6 months); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- 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 accountability, and review dosing diary with the subject; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.

  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)

9.7.19. 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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin is observed during the course of the study, refer to Section 8.4.3.1 to confirm whether an unscheduled safety visit is required.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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

The 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 Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15

- 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 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Liver-related death
- Liver biochemistry (see Table 10 for list of analytes to be tested)
- Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.
- Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (see Appendix C)
- Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) and ELF, (and others as determined during the course of the study).
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Non-Invasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other Secondary Assessments

- OCA (OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide) and C4 will be assayed to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
  - Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

- Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Section 12.1.5 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 13.4) 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 13.4.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definitions of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject 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.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.2. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 9, must be entered on the AE CRF. 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	Causing no limitation of usual activities; the subject may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the subject may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

12.1.4. Reporting of Adverse Events and Serious Adverse Events

12.1.4.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for

duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

12.1.4.2. 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 be reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521
- Telephone: +1 858 964 1571

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:

- Subject 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 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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

The Investigator is responsible for submitting information on 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, 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 12.1.5.

12.1.5. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.

Given that the liver-related 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 liver-related 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 "study event" on the Adverse Event CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.

The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).

12.1.6. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Medical Monitor, 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 subject 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.

12.1.7. 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 12.1.4.2.

All SAEs that occur within 30 days following the cessation of investigational product, 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 12.1.4.2.

SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.

12.1.8. 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 subject 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 subject 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 CRF. 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 subjects 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 CRF. 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.

12.1.9. 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 8.4.2.1) 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 sae@interceptpharma.com or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

The subject 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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 12.1.4 must also be followed.

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening Visit 1, Month 12, and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Dual Emission X-Ray Absorptiometry

A bone density assessment will be done using the DEXA scan.

12.2.6. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their

responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.7. Laboratory Assessments

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

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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 10.

Table 10: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[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	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Blood Sample for Future Analysis	PBC autoantibodies and other cytokines and interleukins TBD
Other	OCA (parent and conjugates [glyco and tauro], OCA-glucuronide) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.9 through pregnancy outcome.

MELD scores, Child-Pugh score, and MRS will be calculated at screening, and at quarterly (MELD and Child-Pugh scores) or semi-annual (MRS) visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to study database lock, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and

span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria where possible.

13.1.2. Determination of Sample Size

The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years subject accrual and 6 years of follow up.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

13.1.2.1. Sample Size Monitoring

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant

- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).
- Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy

The primary efficacy analysis will compare randomized OCA to randomized placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare randomized OCA to randomized placebo in ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.10 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3).

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as

fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time to event secondary efficacy analyses will compare randomized OCA versus randomized placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Progression to cirrhosis will be assessed in the subset of subjects considered non-cirrhotic at baseline using available medical history, clinical, and laboratory assessments as well as baseline TE, where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered non-cirrhotic (See Section 9.7.3.1). Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the trial in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of non-cirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.

Analyses for the histological assessment conducted as part of the biopsy sub-study are defined in Appendix C).

Analyses of changes in MELD score, Child-Pugh score, Mayo Risk Score (MRS), IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.5.1. Association of Biochemistry with Clinical Outcomes and Clinical Benefit

The association between the effect of OCA on ALP and bilirubin and the clinical benefit of OCA will be evaluated by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This analysis will be based on the ITT population.

Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3× ULN and AST ≤2× ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5× ULN and AST ≤1.5× ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67× ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76× ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted,

life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, "where no obvious single optimal external control exists, it may be advisable to study multiple external controls". In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is "similar" to a participating subject. The historical database control should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.3).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment.

Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a full range of covariates across which the treatment and historical controls might differ. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible.

Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation. Therefore, there is no chance of biasing results in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the

estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, hepatocellular carcinoma, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)
- Time to liver transplant or liver-related death
- Time to hepatocellular carcinoma

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), using similar statistical methodology as specified above.

Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.

13.1.9. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

13.1.9.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.9.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.9.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified time point for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.10. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however, hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.11. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) based on the ITT population. Subgroups will be assessed at baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

13.1.12. Continuous Monitoring and Interim Analyses

Blinded safety reports including the accrual of events, drop outs and/or loss of patients to commercially available OCA will be reviewed by the DMC on a regular basis.

Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively.

The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy or futility) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

13.2.4. Cardiovascular Adjudication Committee

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).

13.3. 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 subjects. 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 subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (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 subject safety, which alter the conduct of this study. The Investigators will inform the subjects of such actions and the protocol, patient information sheet (PIS), and consent will be revised, as appropriate.

13.4. Adjudication Committees

All suspected liver-related clinical outcomes, 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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. 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.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 Medical Monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, 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 (when available) 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: The Sponsor, 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.

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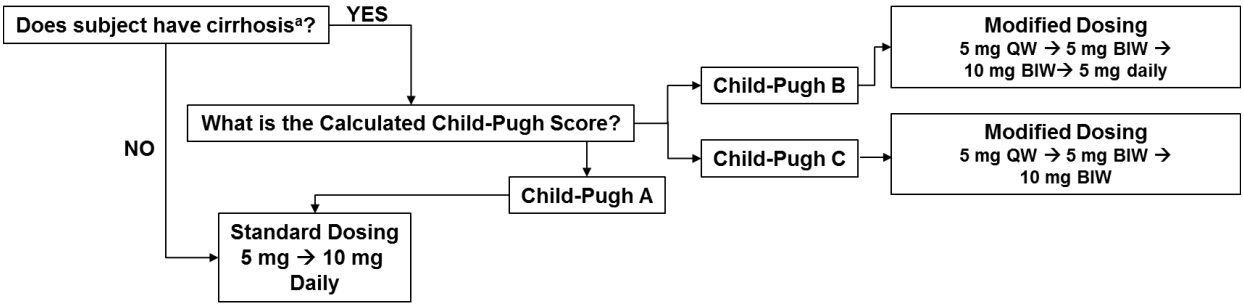
APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT

Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment

An overview of the modified dosing regimen for subjects with Child-Pugh Class B or Child-Pugh Class C is presented in Figure 2 and Table 11.

Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5 mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability and biochemical response. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly.

Figure 2: Dosing by Cirrhosis Status and Child-Pugh Score



[a] Cirrhosis may be assessed by histology or non-histological methods as defined in Section 9.7.3.
BIW = twice weekly; QW = once weekly

Table 11: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Modified Dosing Regimen	
	Child-Pugh B	**Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg once weekly	5 mg once weekly
Titration 1 [b] (≥Month 3)	5 mg twice weekly[c]	5 mg twice weekly[c]
Titration 2 [b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]	10 mg twice weekly[c]
Titration 3 [b] (≥6 weeks after Titration 2)	5 mg daily	NA

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

Modified Dosing Regimen for Subjects with Child-Pugh B Hepatic Impairment

Subjects with cirrhosis and classified as Child-Pugh B at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in Figure 2. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and

following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to twice weekly dosing with 10 mg OCA or matching placebo. Subjects with at least 6 weeks of twice weekly dosing at 10 mg OCA or matching placebo, and meeting dose titration criteria, should up-titrate to the maximum allowed dose of 5 mg OCA or matching placebo once daily.

Investigators may decrease the dosing frequency (back to once or twice weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Modified Dosing Regimen for Subjects with Child-Pugh C Hepatic Impairment

Subjects with cirrhosis and classified as Child-Pugh C at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in Figure 2. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score

Subjects on a modified dosing regimen who demonstrate a change in cirrhosis status and/or Child-Pugh Score should have their dose of investigational product modified to match their current status per the appropriate dosing regimen (see Section 7.4, Table 5); however, changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as changes in status. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change to the dosing regimen. Investigators may contact the Medical Monitor at any time to discuss potential changes to dosing.

Possible scenarios for dosing modifications include:

- Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C
- Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study
- Improvement in classification of Child-Pugh Score from C to B
- Improvement in classification of Child-Pugh Score from B to A; these subjects may be eligible to transition to the standard dosing regimen

Subjects may titrate dose and dosing frequency up or down as appropriate, within the appropriate dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month Post-Titration

Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.10).

Unscheduled Titration Visit, Optional Visit

An unscheduled up-titration visit may be scheduled for as early as 6 weeks after the initial titration visit (or subsequent titration visit) occurs for subjects who are following the modified dosing regimen. The visit procedures required for the unscheduled titration visit are outlined below. Subjects who up titrate at an unscheduled visit will continue to follow the regular visit schedule for all other study visits.

For subjects who up titrate at an unscheduled visit the following procedures will be performed:

- Assess and record AEs.
- Review and record concomitant medications.
- Perform the pre-Titration Tolerability Assessment as outlined in Section 7.4.1.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

For subjects who up titrate at an unscheduled visit: The + 1-week window week related to the 1-Month Post-Titration visit can be extended for up to an additional 5 weeks to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the window is extended past +1 week allowed visit window, at a minimum, a telephone safety contact should then be performed 1-month post-titration.

APPENDIX B. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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Online-Only Content: Audio podcast is available at www.jama.com.

APPENDIX C. BIOPSY SUB-STUDY OF PROTOCOL 747-302: A PHASE 4, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFECT OF OBETICHOLIC ACID ON CLINICAL OUTCOMES IN SUBJECTS WITH PRIMARY BILIARY CHOLANGITIS

The following Protocol Concept is being presented as an Appendix to the current 747-302 Protocol Version 3.1. The final Paired Biopsy Sub-Study Protocol will be provided to participating sites as Addendum 1 to the 747-302 Protocol.

Rationale: The purpose of this sub-study is to assess the effect of OCA versus placebo on the histological severity of disease (fibrosis/cirrhosis) in subjects with PBC. In addition, this sub-study will explore the relationship between histological changes and clinical, laboratory, and non-invasive measures indicative of progression to cirrhosis in patients with PBC.

Population	Subjects must meet all Inclusion and Exclusion criteria for Protocol 747-302 Additional Criteria for the Biopsy Sub-Study are: **Inclusions:** • Must provide written informed consent and agree to comply with the requirements of the sub-study protocol **Exclusions:** • Inability to safely undergo a liver biopsy
Sample Size	N= approximately 45 subjects Assumes 1-sided test 80% power to detect a difference in relative risk of progression to cirrhosis at an alpha of 0.2 when OCA event rate is 0.23 (50% risk reduction 80% power to detect a difference in relative risk of progression to cirrhosis at an alpha of 0.3 when OCA event rate is 0.28 (~45% risk reduction)
Study Design / Duration	Placebo-controlled, randomized, double-blind Participation open to all sites participating in the 747-302 protocol (expectation is approximately 20 sites globally will participate) Placebo, 5-10 mg OCA After meeting all eligibility requirements for this sub-study, subjects will follow the study procedures as outlined in the main protocol for Study747-302. It is expected that subjects will be followed for a minimum of 6 years as in the main protocol. A baseline biopsy must be performed no later than Day 0 (±7 days) unless biopsy was obtained no more than 6 months before Day 1. Timing of post-treatment biopsy: If a subject develops evidence of probable progression to cirrhosis as assessed by the indicators listed below, another biopsy will be performed at that time; biopsy reports and available clinical, laboratory, and radiological assessments will be used as a basis for adjudication by the

	hepatic adjudication committee to assure that all events of progression to cirrhosis meet pre-defined criteria and are consistent across sites. A biopsy will be performed at end of study (EOS) on all subjects who have not already had a biopsy based on evidence of the clinical, laboratory, or radiological indicators of progression during the course of the study.
Primary objectives	To evaluate the effect of OCA compared to placebo on the histological severity of PBC by assessing the following: • Progression to cirrhosis • Improvement in fibrosis/cirrhosis
Secondary objectives	To evaluate the effect of OCA compared to placebo on the histological stage of PBC To demonstrate the relationship between histological changes and clinical, laboratory, and non-invasive measurements indicative of progression to cirrhosis in subjects with PBC including: • Transient Elastography (TE) • Noninvasive scores of liver fibrosis including Enhanced Liver Fibrosis (ELF) and aspartate aminotransferase (AST) to platelet ratio index (APRI),

Indicators of Progression to Cirrhosis informing the timing of biopsy	Persistent (i.e. 2 consecutive measurements obtained at least 3 months apart) elevation in Fibroscan® TE >16.9 kPa
	
	Presence of any of the following:
	• 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 total bilirubin >2x ULN

Biopsies	Paired biopsies will be read by a central reader
Adjudication	Adjudication of progression of cirrhosis will be performed by an independent hepatic adjudication committee as per the main protocol. All available documentation of progression including biopsy reports will be made available to the adjudicators.
Statistical Analysis	For each treatment group, the proportion of subjects with and without biopsy-assessed cirrhosis at the end of study by baseline biopsy-assessed cirrhosis status will be presented in a shift table from Baseline to the end-of-study. For the subset of subjects who were non-cirrhotic at Baseline, Kaplan-Meier (KM) estimates of the time to cirrhosis (as assessed by biopsy) will be summarized and graphed by treatment group. For the subset of subjects who were cirrhotic at Baseline, cumulative incidence estimates of the time to improvement in fibrosis/cirrhosis (as assessed by biopsy) will be summarized and graphed by treatment group.

APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

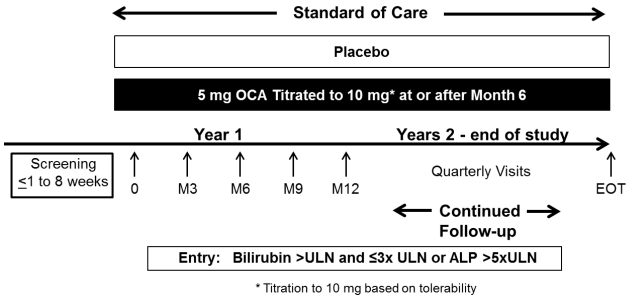
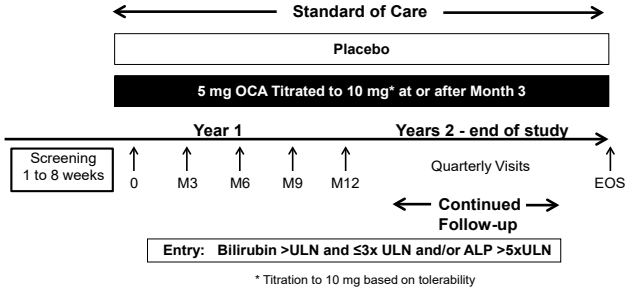
Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: 29 April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact**:** PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD	Contact**:** PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least

Section	Original Text	Revised Text
	2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Section	Original Text	Revised Text
Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5×ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and/**or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12.	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

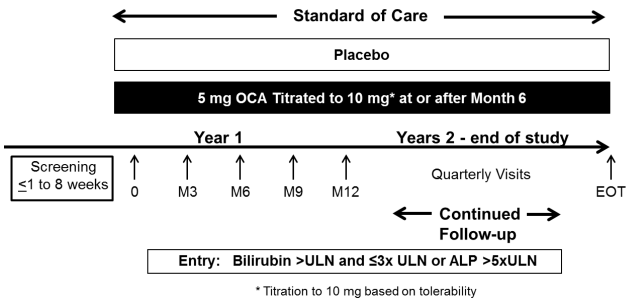
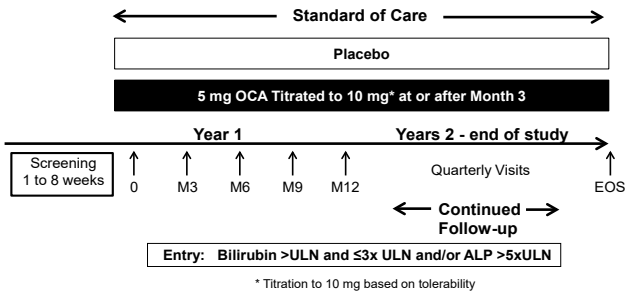
4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>3. Mean total bilirubin >3× ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. Deleted text</td></tr>
<tr><td>Synopsis</td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td>Statistical Methods: Other Efficacy Analyses
• Added text</td><td>Statistical Methods: Other Efficacy Analyses
• Development of varix/varices</td></tr>
<tr><td>4</td><td>List of Abbreviations
Added text</td><td>List of Abbreviations<table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC.</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment.</td></tr>
</table>

Section	Original Text	Revised Text
	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 **up to 4 years.** The **LSTE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete	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**.** The **LTSE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete
5.5.2.1	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.

Section	Original Text	Revised Text
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.**
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….

Section	Original Text	Revised Text
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)*** ***Visit Window ≤1 to 8 wks …*** ***Visit window in 2nd column added new text*** ***Added text*** *Footnote a:* All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on**	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now **"Screening Visit 1"*** *2nd column now **Screening Visit 2*** ***3** to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3*** *Footnote a* All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both**

Section	Original Text	Revised Text
	ALP (ALP >5× ULN), the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3× ULN).**	**analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**.
	Footnote b: The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed	*Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(± 1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.
	Footnote e: Medical history at Screening will smoking and alcohol consumption history and current habits for both.	*Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both.
	Footnote g: **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1)	*Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6)
	Footnote h: Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.	*Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote i: ***Added text***	*Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote j: ***Added text***	*Footnote j*: **Ultrasound will be conducted to enhanced HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	*Footnote k***:** ***Added text***	*Footnote k:* **Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central**

Section	Original Text	Revised Text
		laboratory evaluations per the Child-Pugh scoring system noted in the case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
	Footnote l: ***Added text***	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
	Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change	***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***
7.3	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched

Section	Original Text	Revised Text
	placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5× ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and**/or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile),

Section	Original Text	Revised Text
	contraception during the study and for 30 days after the end of treatment visit.	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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** 4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3× ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**

Section	Original Text	Revised Text
	5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	**5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent. The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text***	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures)**. The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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 potential adjudicated hepatic and/or cardiovascular events**

Section	Original Text	Revised Text
	The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	Concomitant Medications 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 CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to**

Section	Original Text	Revised Text
		continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.
9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical**

Section	Original Text	Revised Text
		Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding. **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.**
9.6	Restrictions **No additional restrictions.**	Restrictions **Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment
</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
<tr><td>EOS
(When subject terminates the study)</td><td>The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject’s</td></tr>
</table>
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</table>

Section	Original Text	Revised Text
		participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study. EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**.	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart

Section	Original Text	Revised Text
	• For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).	• For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of **all available (at least 2; including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs**

Section	Original Text	Revised Text
		• **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours** – **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits** • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the**

Section	Original Text	Revised Text
		screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should**

Section	Original Text	Revised Text
		also be performed when platelet counts are <150 × 10^9 /L.
	• *Added text*	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• *Added text*	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• *Added text*	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**

Section	Original Text	Revised Text
9.7.6	Month 3 Procedures • ***Added text*** • ***Added text***	Month 3 Procedures • **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:** – **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • ***Added text***	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • ***Added text***	Month 9 Procedures • **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**

Section	Original Text	Revised Text
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.12), subjects who are participating in the PK assessment will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments**

Section	Original Text	Revised Text
		○ **Presence/absence of peripheral edema** ○ **Presence (degree)/absence of ascites** ○ **Presence (degree)/absence of hepatic encephalopathy**
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**

Section	Original Text	Revised Text
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will

Section	Original Text	Revised Text
		only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.**
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
		[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7**.**
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.	Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing
	Prior to the EOT Visit:	Prior to the EOT/**EOS** Visit:
	During the EOT Visit:	During the EOT/**EOS** Visit
	• Subject questionnaires (see Section 12.2.6)	• Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)**
	• Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable	• Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
	• ***Added text***	• Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6)
	• ***Added text***	• Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months)
	• ***Added text***	• Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• *Added text*	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline**

Section	Original Text	Revised Text
		(and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of

Section	Original Text	Revised Text
	• ***Added text***	outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:** **a. PBC-40: The PBC-40 (Jacoby 2005) 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.** **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).**

Section	Original Text	Revised Text
		c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
12.1.1.2	Serious Adverse Event • ***Added text***	Serious Adverse Event **Events <u>not</u> 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**

Section	Original Text	Revised Text
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Section	Original Text	Revised Text
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to Appendix C)** and the Sponsor's policies.
19	List of References • Added text	List of References **Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83.** **Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.** **Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629.** **Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.**
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 (DATED 12 NOV 2015)

Rationale

The changes to Amendment 1 of the protocol, detailed below, generated specifically for regulatory authority requests, include an additional exclusion criteria and changes to text precluding UDCA naïve subjects from entering the study and clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, thus answering questions raised by regulatory authorities.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1.1. (Note: Revised text in Amendment 1.1 is indicated in bold font, and the text deleted from Protocol Amendment 1 is crossed out in the table below. Minor formatting changes are not listed.)

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
Title Page	Original: 03 October 2014 Amendment 1: 29 APRIL 2015	Original: 03 October 2014 Amendment 1: 29 **April** 2015 **Amendment 1.1: 12 November 2015**
Study Personnel Contact Information	~~Mobile: PPD (Pacific time zone)~~ Telephone: PPD ~~Telephone~~ PPD	(deleted) Telephone: PPD (deleted)
Synopsis, Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
Synopsis, Statistical Methods: Sample Size Justification	• ~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)
8.3 Subject Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
9.2 Concomitant Medications	(insertion)	**The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile**

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
		of caffeine, a sensitive CYP1A2 substrate, 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.
12.1.4.2 Reporting of Serious Adverse Event	~~Mobile: PPD (Pacific time zone)~~ Telephone: +1 ~~858 964 1571~~	(deleted) Telephone: PPD
13.1.2 Determination of Sample Size	~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)

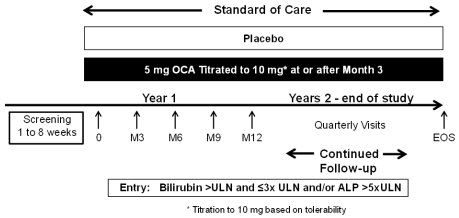
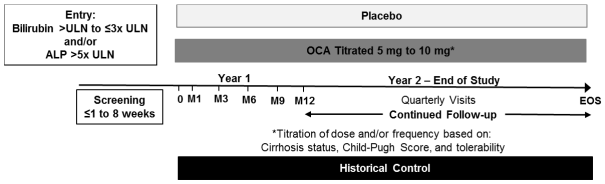
APPENDIX F. SUMMARY OF CHANGES: PROTOCOL VERSION 3 (DATED 07 SEPTEMBER 2016)

Rationale

The changes to Version 3 of the protocol, include dosing adjustments based on Child-Pugh scoring, additional exclusion criteria, changes to text precluding UDCA-naïve subjects from entering the study.

Please note that the Sponsor has renamed protocol "amendments" to "versions", therefore all future revisions that require a revised protocol will have an associated "version" number. The table below includes substantial revisions made to Protocol 747-302 under Version 3, which encompass the revisions captured in Protocol Amendment 1.1. Revised text in Version 3 is indicated in bold font, and the text deleted from Protocol Amendment 1.1 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 (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	... ~~Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups.~~ The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. ~~Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.~~	... Investigational product will be taken orally, once daily **for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C.** The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).	To incorporate a dosing and titration regimen based on subject's Child-Pugh Scores, to align with the recommended dosing regimen found in the Ocaliva US Package Insert for patients with hepatic impairment.

Synopsis, Methodology. 7.1.1, Study Design Diagram, Figure 1	Schematic diagram 	Updated schematic diagram  **Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration**	Incorporate updated dosing scheme to reflect addition of Child-Pugh scoring.
Synopsis, Methodology	(insertion)	**Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:** • **Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.** • **For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.** • **Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should**	Revised methodology to incorporate the changes in dosing for subjects based on the Child-Pugh Scores.

		titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. **Includes New Table: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	
5.1, Overview	(insertion)	**The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication**.	Language updated as OCA is approved in the US with the trade name Ocaliva.
5.5.2.2, Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment	(Insertion)	**New section: Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment** **Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses and those from bile acids in the literature suggest that the doses of OCA administered to hepatically-impaired patients should**	Provide the rationale to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores into the protocol.

		be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure. **Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).**	
5.6, Summary of Known Potential Risks with OCA	(Insertion)	**…These findings were seen more frequently with doses above 10 mg OCA. In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.**	Added two AE terms reported in the updated Investigator's Brochure.
7.1, Overall Study Design	…~~Investigational product will be initiated at 5 mg OCA or matched placebo.~~ Following 3 months of treatment with investigational product, ~~subjects~~ should be titrated ~~in a blinded manner (ie, subjects randomized to OCA will increase their dose to~~ 10 mg OCA) based on tolerability	Investigational product will be taken orally, once daily**. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo.** Following 3 months of **once daily** treatment with investigational product, **the dose** should be titrated **to a maximum** 10 mg OCA **or matching placebo once daily**, based on tolerability (see Section 7.3). **Subjects with cirrhosis and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.**	Amend the protocol to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores.
7.1.2, Table 1, Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2), 9.3,	~~Safety Contact~~	This visit has been deleted.	Replaced with the 1 Month Post-Titration Visit.
	(Insertion)	Added the following visits: • Month 1 • 1 Month Post-Titration Visit	Visits were added to accommodate the updated dosing and titration regimen

Treatment compliance			based on subject's Child-Pugh Scores.
	[b]~~The subject should be contacted by telephone on a monthly basis in between at clinic study visits at Month 1 and Month 2 (± 1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.~~ [e]~~As soon as possible upon study discontinuation and as near as possible to last dose taken.~~ [n]~~Subject to begin dosing on Day 1~~	Deleted.	Result of table being updated for the dosing and titration regimen based on subject's Child-Pugh Scores.
	(Insertion)	Added the following study procedures: • Cirrhosis Status Assessment[e] • Assessments for Child-Pugh Scores[g] • Dose Titration: Standard Dosing[n,o] • Dose Titration: Modified Dosing [n,o] • Dosing Diary	Study procedures were added to accommodate the updated dosing/titration regimen. Dosing diary was added to improve compliance.
	(Insertion)	Added the following footnotes: • **[b]Safety Post-Titration visits must be performed 1 month + 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.** • **[e]Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.** • **[f]Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use**	Added footnotes provide clarity regarding assessments and visits based on the evaluation of Child-Pugh scores.

		data, and peripheral edema assessment data captured in the CRF. • **[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.** • **[n]Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.** • **[o]Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh score (Section 7.3). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.** • **[p]Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet**.	

7.1.2, Table 2, Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)		**New table- Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)**	Divided Schedule of Study Procedures into 2 tables, updated to include visits added per updated dosing/titration information.
7.3, Planned Dosing Regimen	7.3 ~~Treatment Assignment~~ ~~Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3 month study visit or at any study visit thereafter depending on tolerability.~~	**7.3 Planned Dosing Regimen** Subjects will **be randomized to treatment with** either **OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.** **Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).** **For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.**	Section renamed to reflect changes in titration and dosing for subjects with hepatic impairment.
	(Insertion)	**New: Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	

		New: Table 4: Determination of Dosing Regimen	Tables added to clarify changes in titration and dosing.
7.4 Dose Titration Criteria	~~After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA~~ or ~~matched placebo (in a blinded manner) at the 3 month visit or any study visit following the 3 month visit based on~~ tolerability ~~of investigational product~~. ~~For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10 mg dose if tolerated~~	**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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh Score.** **Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.** **Tolerability Dose Titration - Investigators** may decrease **the dosing frequency** or dose **for any subject** at any time during the study, as considered **clinically** appropriate (eg, tolerability; **see Section 7.4.2).** **Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due** to **changes in cirrhosis or Child-Pugh 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.**	Entire section revised to reflect changes in titration and dosing.
7.4 Dose Titration Criteria	(Insertion)	**New: Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score**	

7.4 Dose Titration Criteria	(Insertion)	**Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).** **Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).** **Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.** **Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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 and table added to provide dosing guidelines to investigators.

		Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.	
7.4.1, Pre-Titration Tolerability Assessment Requirements	(Insertion)	**7.4.1 Pre-Titration Assessment Requirements** **Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in study medication (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.** **To be eligible for a dose up-titration:** • **Subjects 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.** • **There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required**	Section added to provide guidance for assessing subject tolerability prior to titration.

8.4.2, Other Reasons for Discontinuation of Study or Investigational Product	(Insertion)	• **Subject begins treatment with commercially available OCA** **… safety concerns and related to study drug** • Consent may be fully withdrawn **(in which case the subject discontinues both investigational product and study visits and procedures)** **…Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.**	Added text as Ocaliva is commercially available in the US and therefore subjects may be discontinued if they began off-study treatment with Ocaliva.
8.4.2.1, Elevated Liver Enzymes	(Insertion)	**New Section: 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.**	Section added to incorporate monitoring of liver test results during the study.

9.1, Investigational Product Treatment Regimen	~~**9.1.1 Dose Adjustment Beginning at Month 3**~~ ~~After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted~~.	**At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.**	Section revised to reflect changes in titration and dosing.
9.2, Concomitant Medications	Subjects taking bile acid sequestrants (BAS) 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).	New sub-heading**:** ***Drug Interactions*** Subjects 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 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.** (…) **Information related to additional drug-drug interaction (DDI) studies is available in the current version of the Investigator's Brochure (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 with OCA that may be observed in study subjects.**	Section revised to provide additional information on drug-drug interactions with OCA.
9.2.1, Prohibited Medications	… the Investigator should be cognizant of the possibility of double dosing ~~and~~	… the Investigator should be cognizant of the possibility of double dosing. **Subjects who continue with**	Ocaliva is commercially available in the US and,

	~~encourage the discontinuation of open-label OCA therapy. However, if~~ commercial OCA therapy ~~remains, then investigational product should be discontinued to avoid potential double dosing~~. ~~Subjects that discontinue investigational product but continue commercial OCA therapy~~ are expected to continue through the end of the study, ~~and~~ the …	commercial OCA therapy **must** discontinue **study medication and** are expected to continue through the end of the study. …	therefore, subjects wishing to take commercially available drug are not discouraged, but they must discontinue study medication.
9.7.1, Visit Windows	(insertion)	**Added the following visit windows:** • **Month 1 (+1 week [7 days])** • **Titration Visit – Standard Dosing Regimen (≥Month 3)** • **Titration Visit 1 – Modified Dosing Regimen (≥Month 3)** • **Titration Visit 2 – Modified Dosing Regimen (≥6 weeks after Titration Visit 1)** • **Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY) (≥6 weeks after Titration Visit 2)** • **Post-Titration Visit, (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency)**	Added visits to accommodate the updated dosing/titration scheme.
9.7.3, Assessing Cirrhosis	(Insertion)	**New: 9.7.3. Assessing Cirrhosis** **To determine which dosing regimen subjects should follow, the presence or absence of 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 is defined as a subject 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)**	Added section to assess cirrhosis as this assessment will determine the acceptable dosing regimen based on a subject's Child-Pugh score.

		• 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/mm3) with:** **– persistent decrease in serum albumin, or** **– elevation in prothrombin time /INR (not due to antithrombotic agent use), or** **– elevated bilirubin (2× ULN)** **Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A).** **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, Child-Pugh Score	(Insertion)	**9.7.4. Child-Pugh Score** **Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh Score includes investigator assessments of ascites and hepatic encephalopathy, which may be**	Section added to provide Investigators with information on the Child-Pugh scoring system.

		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. **It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen**	
9.7.4, Child-Pugh Score	(Insertion)	**Table 6 (New) Child-Pugh Scoring System**	
9.7.6, Screening Procedures (1 to 8 Weeks prior to Day 0)	(Insertion)	The following procedures were added: Screening Visit 1 procedures are as follows: • **Provide the subject with a dosing diary to document his or her dosing** • **Assess for the presence/absence of cirrhosis** • **Perform status assessment for calculation of Mayo Risk Score** Screening Visit 2 procedures are as follows: • **Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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**	Procedures added to assess cirrhosis.

		criteria prior to randomization.	
9.7.7, Day 0 Procedures (Randomization)	9.7.4. ~~Day 0 Procedures~~ ~~• Perform an ultrasound for hepatocellular carcinoma (HCC) surveillance (if equipment is unavailable, …~~ ~~• Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.~~ ~~☐ Presence/absence of peripheral edema~~ ~~☐ Presence (degree)/absence of ascites~~ ~~☐ Presence (degree)/absence of hepatic encephalopathy~~	9.7.7: Day 0 Procedures (Randomization) • **Provide the subject with a dosing diary to document his or her dosing.**	Updated visit to accommodate the updated dosing/titration scheme.
9.7.8, Month 1 Procedures	9.7.5 Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone])	9.7.**8** Month 1 Procedures • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:** - **At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, …** - **If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. …**	Revised section to include the new Month 1 visit procedures.
9.7.9, Month 3 procedures, 9.7.11, Month 6	(Insertion)	• **Perform assessments for calculation of Child-Pugh Score**	Added procedure to accommodate the updated dosing/titration scheme.

Procedures, 9.7.12, Month 9, 9.7.14, Month 12 Procedures			
9.7.9 thru 9.7.17	(Insertion)	**If up-titration will occur at this visit, complete the pre-titration visit and visit related assessments as outlined to ensure all procedures required for dose titration eligibility have been met, including the required review of the dose titration laboratory parameters.** • **Provide the subject with a dosing diary to document his or her dosing** • **… review dosing diary with the subject**	Text added to clarify procedures required before up-titration.
9.7.10, Post Titration Visit Procedures	(Insertion)	New**: 9.7.10. Post Titration Visit Procedures** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.** • **Obtain blood samples for serum chemistry, hematology, and coagulation tests.** • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration visit requirements:** **- At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess**	Added visit to accommodate the updated dosing/titration scheme.

		AEs, review concomitant medications, and assess investigational product compliance. **- If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.** **• Schedule the next visit, reiterate dosing instructions, and advise the subject:** **- 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…**	
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	(Insertion)	**…Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule**.	Clarify that subjects with hepatic impairment may continue to participate in the PK assessment.
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink…	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink **with no other food allowed until after the final 6-hour post dose sample is collected…**	Clarify PK collection procedures.

11.1.2.2, Other Secondary Assessments	• OCA (~~and its conjugates~~) and C4 will be assayed	• OCA **(OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide)** and C4 will be assayed **to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified**.	Clarify the analytes to be measured for the PK analyses.
11.1.2.4, Potential Clinical Outcome Events	(Insertion)	**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 13.4.**	Revised to clarify that potential clinical outcome events meeting the criteria of a SUSAR will not be reported to regulatory authorities expeditiously.
12.1.4.2 Reporting of Serious Adverse Event	In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the ~~medical monitor.~~ All SAEs ~~occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious)~~ must be reported to the ~~medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE~~. SAEs are reported by entering the SAE data into the ~~electronic data capture (EDC) system~~. Entering the SAE data into the EDC system will automatically notify the ~~medical monitor~~ of the event. In the event that the EDC system is inaccessible, an SAE may be reported by ~~telephone or fax~~ using a paper SAE Report form. If an SAE is reported by telephone or fax, an SAE Report form must also be completed in the	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 be reported by: • **E-mail to the SAE email address: sae@interceptpharma.com** • **Fax** using a paper SAE **report** form: **+1 800 497 8521** • **Telephone: +1 858 964 1571** 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	Updated guidance for reporting SAEs.

	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: ~~subject~~ number and ~~initials, a description of the event~~, at least **one** criterion classifying the event as serious and the name and title of the reporting individual. ~~Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting~~ to regulatory authorities by the Sponsor or designee(s). ~~Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible~~. 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. ~~A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).~~ The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) ~~safety reports (SUSARs)~~ that occur during the study within the time frames required by	following information should be provided at the time of the initial report: • **Subject** 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 Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) **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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.** **The Investigator is responsible for submitting information on IND 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND 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 12.1.5.**	

	each regulatory agency. ~~The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).~~ ~~Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities~~		
Section 12.1.5, Suspected Liver-related Clinical Outcome Events	Clinical Outcome Events ~~(Appendix A) as well as Anticipated Events (Appendix B) will not undergo~~ expeditous reporting.	**12.1.5 Suspected Liver-Related Clinical Outcome Events** **Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.** **Given that the liver-related clinical outcome events could also meet the criteria of a SUSAR, please refer to Section 11.1.2.4.** **The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred**	Updated section to account for events related to hepatic impairment**.**

		term: hepatic encephalopathy), spontaneous bacterial and peritonitis (preferred term: peritonitis bacterial).	
13.2.4, Cardiovascular Adjudication Committee	13.2.3 (…) In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study ~~and will be described separately~~.	**New Section: Cardiovascular Adjudication Committee** In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. **Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).**	Committee added to assess cardiovascular events in subjects during the study.
13.4, Adjudication Committee	All ~~potential endpoint events~~ will be reviewed by ~~an~~ adjudication committee before inclusion in the any analysis. The ~~adjudication of potential clinical endpoint~~ events will include, ~~but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership~~, the reporting of events by the	All **suspected liver-related clinical outcomes, 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**	Committees added to assess liver impairment in subjects during the study.

	study site, ~~reporting~~ of the ~~final assessment,~~ supply of source documentation to the committee, ~~the~~ review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members ~~will remain blinded to treatment group throughout the study~~. ~~In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.~~	**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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.**	
Appendix A, Modified Dosing Regimen for Subjects with Child-Pugh B/C Hepatic Impairment	(Insertion)	New**: APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT**	Added section to describe changes in dosing and titration for subjects assessed as cirrhotic Child-Pugh B or Child-Pugh C.
Appendix B, LIST OF STUDY 747-	Was Appendix A	Now Appendix B	The hepatic dosing appendix became Appendix B

302 OUTCOME EVENTS			
Appendix C	~~LIST OF STUDY 747-302 ANTICIPATED EVENTS~~	Deleted	Replaced by Appendix B, more comprehensive description of the outcome events.

APPENDIX G. SUMMARY OF CHANGES: PROTOCOL VERSION 3.1 (DATED 23 DECEMBER 2016)

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the expansion of the spectrum of stages of PBC disease, the addition of progression to cirrhosis as a secondary endpoint, and the addition of two interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

The following table includes revisions that were made to Protocol Version 3.1 with an associated reason or justification for the change. Rationales (Justifications for Change) that impact multiple sections are provided below and referenced in the table with the appropriate rationale number.

1. The phase of the study has been changed from '3b' to '4' to reflect that this is a post-marketing study.
2. The term 'primary biliary cirrhosis' has been changed to 'primary biliary cholangitis' throughout the document to reflect recent changes in nomenclature for PBC.
3. The increase in number of required events from 121 to 127 is due to the addition of two interim analyses (IA), which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy or futility) of the study. One IA will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). Inclusion of patients with earlier stage disease will also increase the time to event requiring more events in order to keep follow-up to approximately 6 years.
4. The first year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by two years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.

5. 'Encephalopathy' has been modified to 'Hepatic Encephalopathy' to clarify that the relevant clinical outcome enApdpoint should be related to hepatic disease.

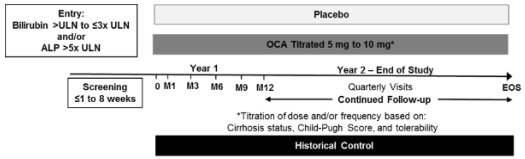
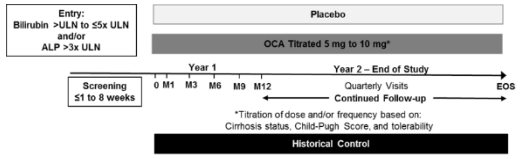
6. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of Hepatocellular Carcinoma.

7. **Broadening the Spectrum of Disease**: Lowering the minimum allowable baseline ALP to 3x ULN and raising the maximum allowable baseline total bilirubin to 5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the phase 3 protocol 747-301.

8. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
9. The increase in enrollment from 350 to 428 is due in part to the increased number of events, and in part due to the change in the estimated Placebo baseline hazard rate which resulted from changing the lower limit of ALP from 5× ULN to 3× ULN in the enrollment criteria #2.
10. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential non-invasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of 302.

The text deleted from Protocol Version 3 is crossed out while revised text in Version 3.1 is indicated in bold font in the table below. Minor/editorial changes and non-substantial changes are not listed individually in the summary table below.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD	**Or if Not Available:** Contact: PPD **MD, PhD Medical Director, Clinical Research,** Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	Back-up medical monitor responsibilities were transferred to PPD
Synopsis, Studied Period (years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	~~3b~~	**4**	Rationale 1
Synopsis, Objectives, Primary,	• Encephalopathy (as defined by a West Haven score of ≥2)	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5

Statistical Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities	• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities **unless confirmed by biopsy**	Rationale 6
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***Insertion*** To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects	**To assess the effect of OCA compared to placebo on progression to cirrhosis** To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 6
Synopsis, Methodology: Schematic Diagram Section 7.1.1 Study Design Diagram, Figure 1	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. • Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product. • Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose	Rationale 7 Rationale 8

	of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (planned)	Approximately ~~350~~ subjects	Approximately **428** subjects	Rationale 9
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ≤~~3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 7
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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: • ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~ • Intrauterine device (IUD)~~; or~~	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below: • **Barrier** method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide • Intrauterine device (IUD)	Standardizing language across protocols; removing double-barrier terminology

<table>
<tr><td></td><td>• 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 subject</td><td>• Vasectomy (partner)
• Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
• Abstinence, if in line with the preferred and usual lifestyle of the subject</td><td></td></tr>
<tr><td>Synopsis, Exclusion Criteria
Section 8.3 Subject Exclusion Criteria</td><td>3. Mean total bilirubin >~~3~~x ULN</td><td>Mean total bilirubin >**5**x ULN</td><td>Rationale 7</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities</td></tr><tr><th>Secondary Objectives</th><th></th></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities **already confirmed by biopsy**</td></tr><tr><th>Secondary Objectives</th><th></th></tr><tr><td>**Progression to cirrhosis**</td><td>**Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated**</td></tr></table></td><td>Rationale 5

Rationale 10</td></tr>
<tr><td>Synopsis, Statistical Methods
Analysis Populations</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control.</td><td>Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population.</td></tr>
</table>

	Control. Descriptions of subject populations are provided in Section 13.1.1.	Descriptions of subject populations are provided in Section 13.1.1.	
Synopsis, Statistical Methods, Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints.	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints.	
Synopsis, Statistical Methods, Other Efficacy Analyses Section 13.1.5 Additional Secondary Efficacy Analyses	***Insertion***	**Progression to cirrhosis will be assessed in the subset of subjects considered non-cirrhotic at baseline using available medical history, clinical, and laboratory assessments as well as baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered non cirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the trial in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of non-cirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.**	Rationale 10

		Analyses for the histological assessment conducted as part of the biopsy sub-study are defined in Appendix C.	
Synopsis, Statistical Methods, Safety Analyses	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will ~~compare OCA and placebo using~~ the Safety Population.	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will **be summarized by treatment group for** the Safety Population.	Clarification of summary analyses
Synopsis, Statistical Methods, Sample Size Justification	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Rationale 3
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up • ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **subject** accrual and 6 years of follow up • **Two interim analyses and one final analysis are planned** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Rationale 4 Rationale 3

	In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	
Section 5.6 Summary of Known Potential Risks with OCA	~~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).~~ ***Insertion***	**An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg and in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies.** **Refer to the IB for additional information regarding the known potential risks with the investigational product.**	Language has been updated to reflect Sponsor standards
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~ year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3). The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5**× ULN or ALP >**3**× ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**….based on tolerability **and biochemical response** (see Section 7.3) The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 1 Rationale 9 Clarification Rationale 7 Rationale 3
Section 7.1.2 Schedule of Study	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration**	Physical Exams have been added one month after each

Procedures, Table 1		• **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	dose adjustment for added safety monitoring.
	[j] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments at Day 0 and Month 12)
	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	[m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds**: unless HCC has already confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
	[o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. …	[p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. …	Rationale 8
	[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a baseline (e.g. Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.**	Clarification

Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions*** [i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~ Not required if done within ~~6~~ months of visit. ***Insertion*** (subsequent footnotes are renumbered accordingly) [j] Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up** [i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. Not required if done within **3** months of visit [j] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Not required if done within 6 months of visit.** [k] Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: **unless HCC has already been confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments) Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study.	Rationale 9
Section 7.3 Planned Dosing Regimen	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the	Rationale 8

	the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score ***Footnotes were re-ordered*** [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin >ULN**. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	
Section 7.4 Dose Titration Criteria	***Insertion***	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.**	Added language to clarify titrations (up or down)

Section 8.4.1.1 Severe Drug-Induced Liver Injury	***Insertion***	**If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. Subjects who develop significant drug-induced liver injury which is considered 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, evidence of 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.** **Severe drug induced-liver injury that is not considered related to investigational product must be discussed with the Sponsor before investigational product is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time.**	Added guidelines for subjects who develop severe Drug-Induced Liver Injury

		All suspected drug-related hepatic injury events will be adjudicated by the Hepatic Safety Committee (see Section 13.4).	
Section 8.4.1.2 Liver Transplantation	***Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product***	**8.4.1.2 Liver Transplantation** **Subjects must discontinue investigational product after undergoing liver transplantation surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection.**	The relocation of this statement from within Section 8.4.2 to 8.4.1.2 clarifies directions to discontinue subjects who undergo a liver transplant from investigational product but not study visits
Section 8.4.2 Reasons for Mandatory Interruption of Investigational Product	***Insertion/Reorganization***	**8.4.2 Reasons for Mandatory Interruption of Investigational Product** **Prior to re-starting investigational product after a prolonged interruption, the subject must be re-consented and new baseline visit procedures must be performed if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.**	This clarifies what should be done when a subject experiences a prolonged interruption in investigational product such as in the event of pregnancy
Section 8.4.2.1 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be~~	**8.4.2.1 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product **immediately,** but should continue with the study visit schedule. **As described in Section 12.1.9** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.9). New baseline procedures should include pregnancy testing.**	Language simplified and aligned with Sponsor standards

	~~permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~		
Section 8.4.3 Other Reasons for Discontinuation of Study of Investigational Product	8.4.2 Other Reasons for Discontinuation of Study of Investigational Product Subjects ~~that~~ discontinue investigational product are expected to continue in the study until the end of the study~~, and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ or at the discretion of the Sponsor.~~ If~~ a subject~~ reaches an event,~~ he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who ~~choose to~~ discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and the study will only terminate~~ (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or cardiovascular events~~. ~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects should be encouraged to consent to the semiannual telephone contact and/or continued record review only to~~	**8.4.3** Other Reasons for Discontinuation of Study of Investigational Product 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. **With the exception of liver transplant, if** a subject **experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor): – 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), liver-related clinical outcomes, and drug-related hepatic injury events.** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	Discontinuation of investigational product language updated to clarify the process that is to be followed after discontinuation and instruct subjects to continue regular visit schedule.

	~~allow for secondary outcome events data to be collected.~~		
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** To determine which dosing regimen subjects should follow, the presence or absence of 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~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as non-cirrhotic at baseline per the criteria listed in Section 9.7.3.1 exhibits any of those same criteria (excluding biopsy results consistent with PBC Stage 4), the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites participating in the paired biopsy sub-study (see** Appendix C**) must confirm progression to cirrhosis by biopsy. All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	Provides detail around the assessment of Progression to Cirrhosis as a secondary endpoint
Section 9.7.6 Screening Procedures	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN).	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5**× ULN and/or an ALP >**3**× ULN).	Reflects new inclusion criteria

Section 9.7.7 Day 0 Procedures	• Perform transient elastography ~~(TE; at selected study sites, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Perform transient elastography **at all study sites with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	Clarifies use of TE and modifies the time during which an historic TE report remains valid
Section 9.7.8 Month 1 Procedures Section 9.7.10 Post-titration visit Procedures	***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:	• **Perform a physical examination.** – In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit **laboratory** requirements:	Physical examinations 1 month after initiating dosing with investigational product will enhance safety monitoring Returning to the site for monthly laboratory assessments can present a significant burden on subjects, thus alternatives are provided for collecting lab samples; with the addition of the physical exam as well the requirement for these exams is provided in the context of the alternatives for laboratory specimen collection
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion***	• **Perform a physical examination** • **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	TE assessment has been added as biannual assessment at all study sites with access to Fibroscan® TE device Hepatic ultrasound should be performed biannually per AASLD and EASL guidelines for subjects with PBC
Section 11.1.2 Secondary Assessments	***Insertion***	• **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.**	Rationale

		• **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (see Appendix C)**	
Section 11.1.2.4 Potential Clinical Outcome Events	The events listed in ~~Appendix A~~ will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	The events listed in **Section 12.1.5** will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	Appendix referencing clinical outcomes events was removed due to redundancy
Section 12.1.4.2 Reporting of Serious Adverse Events	***Insertion***	**Redacted medical record source documentation will be requested for all SAEs and emergency room visits.**	Added sentence regarding redacted medical records to align with Sponsor safety standards
Section 12.1.5 Suspected Liver-Related Clinical Outcome Events	~~For~~ liver-related clinical outcome events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, ~~please refer to Section 11.1.2.4.~~ The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred	**Given that the** liver-related 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 liver-related 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 "study event" on the Adverse Event CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.** The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy	Updated to align with modified standard safety procedures and Sponsor standard language

	term: hepatic encephalopathy), and spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).	(preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).**	
Section 12.1.7 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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours).	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 12.1.4.2.	Updated to align with modified safety procedures and Sponsor standard language
Section 12.1.8 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. 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.**	Updated to align with modified standard safety procedures and Sponsor standard language
Section 12.1.9 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~~ investigational product and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing~~ or ~~emailing~~ to ~~the Sponsor at~~ +1 800 497 8521 or sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may~~	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 8.4.2.1) 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** sae@interceptpharma.com **or faxed to** +1 800 497 8521. **The subject and neonate must be followed for outcome information**	Updated to align with modified standard safety procedures and Sponsor standard language

<table>
<tr>
<td></td>
<td>~~also follow the health of an infant born subsequent to use of investigational product.~~

The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see~~ Section 8.4.1~~).~~</td>
<td>and/or as considered appropriate by the Investigator and Sponsor.

The subject may re-start 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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 12.1.4 must also be followed.</td>
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<tr>
<td>Table 10 List of Laboratory Analytes</td>
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<tr><td>~~Measurement of Liver Fibrosis~~</td><td>~~Fibroscan~~</td></tr>
<tr><td>~~Bone Density Assessment~~</td><td>~~DEXA~~</td></tr>
<tr><td>Other</td><td>Insertion</td></tr>
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<td>Deletion

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<tr><td>Other</td><td>OCA-glucuronide</td></tr>
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<td>Measurements of liver fibrosis are captured in a different section

OCA-glucuronide was listed in the text but missing from the table</td>
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<tr>
<td>Section 13.1.1 Analysis Populations</td>
<td>• ~~The Randomized Population will include all randomized subjects~~</td>
<td>Deletion</td>
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<tr>
<td>Section 13.1.2.1 Sample Size Monitoring</td>
<td>9.1.2.1 Sample Size~~ Re-Estimation Plan~~

~~Therefore, starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a <u>blinded</u> manner quarterly. This evaluation will determine if any</td>
<td>9.1.2.1 Sample Size Monitoring

Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a <u>blinded</u> manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain</td>
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	increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups. ~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.~~ ~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~	a total of **127** adjudicated events for the final analysis in the combined groups. ***Deletion***	
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between the effect of OCA on ALP and bilirubin and the clinical benefit of OCA will be evaluated by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This analysis will be based on the ITT population.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.

		This analysis will be further described in the SAP.	
13.1.8 Supportive Analysis	***Insertion***	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1), using similar statistical methodology as specified above.** **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the Sponsor has received agreement from regulatory authorities.
Section 13.1.9 Alternative Primary Analysis	~~13.1.9 Alternative Primary Analysis~~ ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section **13.1.2.1**). Similar statistical methodology as specified above in Section **13.1.8** for supportive analyses will be utilized.~~ ~~The propensity score quintile will be then be used as the stratification factor in the stratified log-rank test to compare groups. 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~~	***Deletion***	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the Sponsor has received agreement from regulatory authorities

	~~estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section **13.1.8** will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~ ~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs and/or loss of patients to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy or futility) of the study beyond each**	Explanation of the type of review that will be ongoing by the DMC during study conduct.

		interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.	
Section 19 List of References	***Insertion***	**Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	Additional relevant references were added.
Appendix B List of Study 747-302 Outcome Events	~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~	**Deleted**	Redundant; Information is contained within the protocol

	~~Spontaneous bacterial peritonitis~~ ~~Ascites~~ ~~Hepatocellular carcinoma~~		
Appendix C Biopsy Sub-Study of Protocol 747.302: A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in subjects with Primary Biliary Cholangitis	***Insertion***	**See Appendix C**	The purpose of this sub-study is to assess the effect of OCA versus placebo on the histological severity of disease (fibrosis/cirrhosis) in subjects with PBC. In addition, this sub-study will demonstrate the relationship between histological changes and clinical, laboratory, and non-invasive measures indicative of progression to cirrhosis in patients with PBC.

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Version 4: 10 May 2017

EudraCT Number: 2014-005012-42

Sponsor

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

TEL: +1 858 250 6398

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD PhD

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

10 May 2017
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 747-302. 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor – 24-hour Emergency Reporting

Contact**:**	PPD MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.
Mobile:	PPD (Pacific time zone)
Telephone:	PPD
Email:	PPD
SAE Fax:	+1 800 497 8521
SAE Email:	sae@interceptpharma.com

2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid (OCA)

Name of Active Ingredient:

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

Title of Study:

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

Investigators and/or Study Center(s):

Approximately 170 investigational study sites, globally.

Studied Period (Years):	**Phase of Development:**
The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Phase 4

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cholangitis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above.

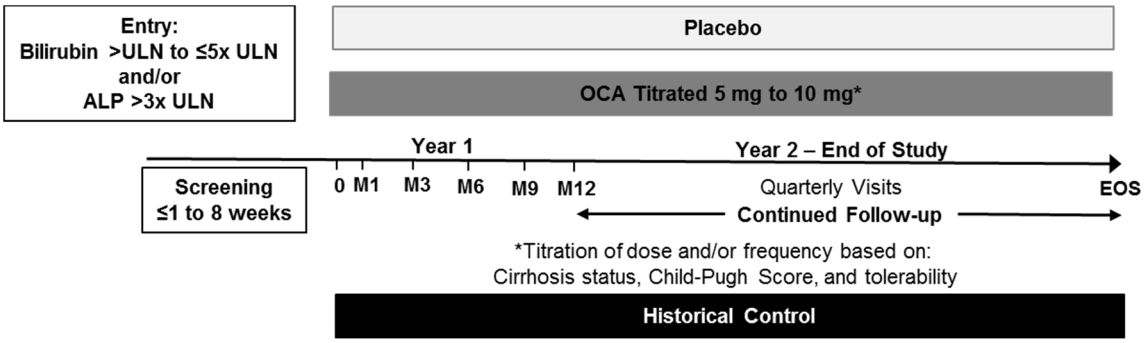
To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.

To assess the effect of OCA compared to placebo on progression to cirrhosis.

To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes. To characterize the pharmacokinetics (PK) of OCA and its conjugates in a subset of subjects. To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo. To assess the safety and tolerability in subjects treated with OCA compared to placebo.
Methodology: This Phase 4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened twice during a 1- to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.6). Investigational product will be taken orally, once daily for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (> upper limit of normal [ULN]/ ≤ULN). A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening. **Schematic Diagram Study 747-302:**    EOS = end of study; ULN = upper limit of normal Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN). Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below: • Noncirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product. • For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. • Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability and biochemical response. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability and biochemical response.

Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Planned Dosing Regimen		
	Standard	Modified	
	Noncirrhotic/ Child-Pugh A	Child-Pugh B	Child-Pugh C
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly	5 mg twice weekly
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly	10 mg twice weekly
Titration 3 [b] (≥6 weeks after Titration 2)	NA	5 mg daily	NA

[a] Starting dose based on subject's cirrhosis status and Child-Pugh Score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.

Number of Subjects (Planned):

Approximately 428 subjects are planned to be enrolled in the study. In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
   - Intrauterine device (IUD)
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence, if in line with the preferred and usual lifestyle of the subject
6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy
     – Spontaneous bacterial peritonitis
   - Known or suspected HCC
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (Visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)
3. Mean total bilirubin >5x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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-month 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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
14. UDCA naïve (unless contraindicated)

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Reference Therapy, Dosage and Mode of Administration:

Placebo (matching tablets)

Duration of Treatment:

It is expected that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 127 total primary endpoint events.

Criteria for Evaluation:

Primary Objectives	**Assessments**
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Progression to cirrhosis	Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (ie, Fibroscan® transient elastography [TE]) confirmed by biopsy unless not medically indicated
HCC	Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy
Change in baseline liver biochemistry	Liver biochemistry (see Table 11 for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhanced liver fibrosis (ELF), and Fibroscan® TE
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
PK	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events Clinical laboratory values

Statistical Methods:

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP), Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBC Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Efficacy Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

All events will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 its 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Additional Secondary Efficacy Analyses

The following time-to-event secondary efficacy analyses will compare OCA versus placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)

- Time to development of varix/varices
- Progression to cirrhosis
- Time to occurrence of HCC
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as Baseline TE where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at Baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.

For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2.

Further details on efficacy, health outcomes, and PK analyses are specified in Section 13.

Safety Analyses

Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will be summarized by treatment group for the Safety Population.

Sample Size Justification

The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN. The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years of subject accrual and 6 years of follow-up
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.
- A dropout rate of 10% is assumed.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
CAC	Cardiovascular Adjudication Committee
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DEXA	dual-emission X-ray absorptiometry
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
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FIS	Fatigue Impact Scale
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	Investigator's 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
LDL	low-density lipoprotein
LTSE	long-term safety extension
MACE	major adverse cardiovascular events
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SUSAR	suspected unexpected serious adverse reaction
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event

Abbreviation or Specialist Term	Explanation
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 Primary Biliary Cholangitis and Obeticholic Acid

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 United States (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.

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), 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 (Pellicciari 2002). 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. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

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

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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.

[1] Includes estimated numbers from ongoing blinded studies.

Study 747-301 (216 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects reaching specific criteria for ALP and bilirubin (ALP <1.67× 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 <1.67× 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 10 mg OCA 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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rationale for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. As a result, starting subjects on 5 mg OCA and titrating to 10 mg based on tolerability and clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate

biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Dose

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study (Study 747-301) subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus. Based on these data, the approved dosing regimens for OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose for at least 3 months, increasing to 10 mg OCA, if tolerated.

5.5.2.2. Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh Score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic

impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).

5.5.2.3. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Summary of Known Potential Risks with OCA

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, but with a much lower frequency than that observed in subjects 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 subjects 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 (HDL) and an increase in low density lipoprotein (LDL). Notably, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.

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

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above.

To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.

To assess the effect of OCA compared to placebo on progression to cirrhosis.

To assess the effect of OCA compared to placebo on time to occurrence of HCC.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To characterize the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 4, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤5x ULN and/or ALP >3x ULN. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 428 subjects meeting all enrollment criteria will be recruited into the study over an approximate 4-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). Subjects will be screened during a 1- to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.6). Randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening. In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used.

Subjects will be dosed according to their cirrhosis status and Child-Pugh Score. Subjects who are noncirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo. Following 3 months of once daily treatment with investigational product, the dose should be titrated to a maximum 10 mg OCA or matching placebo once daily, based on tolerability and biochemical response (see Section 7.3).

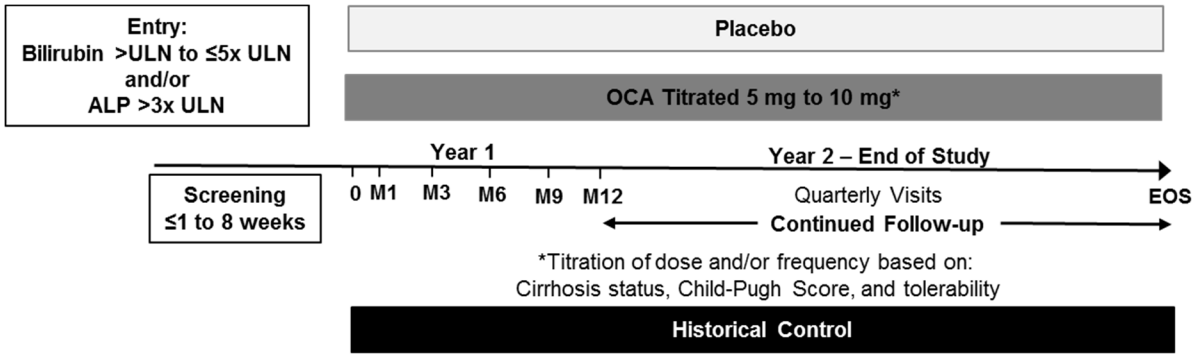
Subjects with cirrhosis (see Section 9.7.3) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.

It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 127 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.

This study will be conducted at approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; ULN = upper limit of normal
Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (Up-titration should be considered when ALP and/or total bilirubin are >ULN). Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2)

	Screening Visits		Day 0	M 1	M 3	1-Month Post-Titration Visit[b]	M 6	M 9	M 12
	1	2[a]							
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Informed Consent	X								
Medical/PBC History[d]	X								
Cirrhosis Status Assessment[e]	X								
Inclusion/Exclusion Criteria	X	X	X						
Physical Exam	X			X		X	X		X[d]
Assessments for Mayo Risk Score[f]	X						X		X
Assessments for Child-Pugh Score[g]	X				X		X	X	X
Vital Signs (including weight)	X[h]		X		X		X	X	X[h]
12-Lead Electrocardiogram	X								X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X				X		X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[i]			X						X
Fibroscan® TE[j]			X				X		X
DEXA[k]			X						X
Endoscopy[l]			X						X
Hepatic Ultrasound[m]		X					X		X
Adverse Events	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Health Outcome Assessments[n]			X		X		X	X	X

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2) (Continued)

	Screening Visits		Day 0	M 1	M 3	1-Month Post-Titration Visit[b]	M 6	M 9	M 12
	1	2[a]							
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Randomization/Treatment Assigned			X						
Dose Titration: Standard Dosing[o,p]					X		X (if applicable)		
Dose Titration: Modified Dosing (if applicable)[o,p]					X		X	X	X
Dispense Investigational Product[q]			X		X		X	X	X
IP Accountability/Compliance				X	X	X	X	X	X
Dosing Diary			X	X	X	X	X	X	X
LABORATORY EVALUATIONS[r]									
Urinalysis	X		X						X
Urine-based β-hCG Pregnancy Test[s]	X		X						
Chemistry/Hematology/Coagulation	X	X[a]	X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X		X		X	X[t]	X
Markers of Hepatic Fibrosis and/or Inflammation[u]			X				X		X
Genetics[v]			X						X
Blood Sample for Future Analysis[w]			X				X		X

AE = adverse event; ALP = alkaline phosphatase; β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; eCRF = electronic case report form; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] Post-Titration visits must be performed 1 month (+ 1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.
[e] Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.
[f] Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the eCRF.
[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] Height will be collected at this visit.
[i] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).
[j] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.
[k] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.
[l] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed window at Day 0 for this specific procedure.
[m] 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.
[n] Health Outcome Assessments: Data related to nonstudy related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.
[o] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.
[p] Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh Score (Section 9.7.4). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.
[q] Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.
[r] The subject 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.
[s] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at the central laboratory. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
[t] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.13 for the PK sampling schedule.
[u] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.
[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. If a Baseline (eg, Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.
[w] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2)

	Year 2 Through End of Study					
	M 3 continued follow-up	**1-Month Post-Titration Visit[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**+1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Physical Exam[d]		X			X	X
Assessment for Mayo Risk Score[e]			X		X	X
Assessments for Child-Pugh Scores[f]	X		X	X	X	X
Vital Signs (including weight)			X		X[g]	X[g]
12-Lead Electrocardiogram					X	X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[h]					X	X
Fibroscan®TE[i]			X		X	X
DEXA[j]					X	X
Endoscopy[k]					X	
Hepatic Ultrasound[l]			X		X	X
Adverse Events	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Health Outcome Assessments[m]	X		X	X	X	X
Dose Titration (if applicable)[n,o]	X		X	X	X	
Dispense Investigational Product	X		X	X	X	
IP Accountability/Compliance	X	X	X	X	X	X
Dosing Diary	X	X	X	X	X	X
LABORATORY EVALUATIONS[p]						
Urinalysis					X	X
Chemistry/Hematology/Coagulation	X	X	X	X	X	X

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2) (Continued)

	Year 2 Through End of Study					
	M 3 continued follow-up	**1-Month Post-Titration Visit[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**+1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
OCA, C4, and FGF-19 (plasma)					X	X
Markers of Hepatic Fibrosis and/or Inflammation[q]			X		X	X
Genetics[r]					X	
Blood Sample for Future Analysis[s]			X		X	X

AE = adverse event; β-hCG = beta human chorionic gonadotropin; DEXA = dual-emission X-ray absorptiometry; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency. Post-titration visits must be performed 1 month ± 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment.

[b] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] The yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.

[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 case report form.

[g] Height will be collected at this visit.

[h] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.6).

[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available.

[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available.

[k] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices.

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

[m] Health Outcome Assessments: Data related to nonstudy related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[n] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[o] Dose Titration is based on cirrhosis status (see Section 9.7.3) and Child-Pugh Score (Section 9.7.4). The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

[p] The subject should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, but water is permitted.
[q] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.
[r] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.
[s] Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 428 subjects will be randomized in the study to achieve 127 adjudicated primary endpoint events. In the event additional subjects are needed to complete enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

7.3. Planned Dosing Regimen

Subjects will be randomized to treatment with either OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.

Subjects who are noncirrhotic or classified as Child-Pugh A at screening will receive 5 mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product and assessment of biochemical response. Up-titration should be considered when ALP and/or total bilirubin are >ULN. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).

For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.

Table 3: Planned Dosing Regimen by Cirrhosis and Child Pugh Score

	Scheduled Dosing Regimen		
	Standard	**Modified**[a]	
	Noncirrhotic/ Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Starting Dose[b] (Day 0)	5 mg daily	5 mg once weekly	5 mg once weekly
Titration 1[c] (≥Month 3)	10 mg daily	5 mg twice weekly[d]	5 mg twice weekly[d]
Titration 2[c] (≥6 weeks after Titration 1)	NA	10 mg twice weekly[d]	10 mg twice weekly[d]
Titration 3[c] (≥6 weeks after Titration 2)	NA	5 mg daily	NA

[a] Refer to Appendix A for additional instructions regarding subjects following the Modified Dosing Regimen.
[b] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening.
[c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4).
[d] Dosing per the twice weekly schedule must be at least 3 days apart.

The dosing regimen should be determined as described in Table 4. Investigators should follow the dosing/titration schedule as shown in Table 3.

Table 4: Determination of Dosing Regimen

Cirrhosis?	No	Yes	Yes	Yes
Child-Pugh Score	Any	A	B	C
Dosing Regimen	Standard		Modified for Child-Pugh B	Modified for Child-Pugh C

7.4. Dose Titration 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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh 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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.

Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier

than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability; see Section 7.4.1).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due to changes in cirrhosis or Child-Pugh 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, biochemical response, and clinical judgment.

Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score

Original Status	New Status[a]		
	Noncirrhotic *OR* Child-Pugh A	**Child-Pugh B**	**Child-Pugh C**
Noncirrhotic or Child-Pugh A	*No Change*	10 mg daily → 5 mg daily 5 mg daily →No change **or** 10 mg twice weekly[b]	5 mg or 10 mg daily → 10 mg twice weekly[b]
Child-Pugh B	5 mg daily → 10 mg daily	*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 weeklyb → No change **or** 5 mg once weekly
Child-Pugh C	10 mg twice weekly → 5 mg daily	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 subject begins dosing with the new dosing regimen, titration should occur as described for that dosing regimen in Section 7.3 or Appendix A.
[b] Dosing per the twice weekly schedule must be at least 3 days apart.

Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the Investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).

Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate

dosing regimen. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).

Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.

Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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.

Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in study medication (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.

To be eligible for a dose up-titration:

- Subjects 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.
- There must be no clinically significant increase (as determined by the Investigator) in the subject's liver function tests.

7.5. Criteria for Study Termination

The Sponsor 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 DMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at

an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 127 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.
2. A mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects of child-bearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
   - Intrauterine device (IUD)

- Vasectomy (partner)
- Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
- Abstinence, if in line with the preferred and usual lifestyle of the subject

6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy
     – Spontaneous bacterial peritonitis
   - Known or suspected hepatocellular carcinoma
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 μmol/L)
3. Mean total bilirubin >5x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
14. 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 to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be adjusted back to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.

Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.

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

Subjects 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. Subjects with

persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or international normalized ratio (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 >3x baseline (and >ULN)
- Total bilirubin >2x 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 AE information should also be collected and the subject 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 >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 study medication and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject 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.

If at any time a subject 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.

Subjects who develop evidence of severe drug-induced liver injury, which 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 subjects 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 subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.

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 13.4).

8.4.1.3. Pregnancy

If a female subject becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 12.1.11 pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 12.1.11.

8.4.2. Reasons for Mandatory Discontinuation of Investigational Product

8.4.2.1. Liver Transplantation

Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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 subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor):

- Subject begins treatment with commercially available OCA
- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.

- 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 subject 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 subject withdraws consent (See Section 9.7.18).

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

8.4.4. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.5. Lost to Follow-Up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.6. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.18, Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or matching 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 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, up to once daily, for the duration of the study.

All subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Drug Interactions

Subjects 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 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 Investigator's Brochure (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 with OCA that may be observed in study subjects.

PBC-Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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. Subjects who continue with commercial OCA therapy must discontinue study medication and are expected to continue through the end of the study (see Section 9.7.18). The study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (see Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).

9.3. Treatment Compliance

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

Subjects should be instructed to complete a dosing diary to help monitor compliance to the prescribed dosing regimen. Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable, follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to one of two treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2 below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects 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 subject). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the subject'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 subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The Data Monitoring Committee (DMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded subject data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the trial 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 Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0. The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening Visit 1 interval is 3 to 8 weeks prior to Day 0. Screening Visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window. See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Month 1	+1 week (7 days)
Titration Visit – Standard Dosing Regimen	≥Month 3
Titration Visit 1 – Modified Dosing Regimen	≥Month 3
Titration Visit 2 – Modified Dosing Regimen	≥6 weeks after Titration Visit 1
Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY)	≥6 weeks after Titration Visit 2

Visit or Procedure	Visit Window and/or Interval
Post-Titration Visit	1 month (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency
Month 3 to Month 12	±2 weeks (14 days)
Quarterly visits (Months 15 to EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study.

EOS = end of study; EOT = end of treatment

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of / study to the subject and will provide him/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Assessing Cirrhosis

9.7.3.1. Determination for Dosing Regimen

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

- Biopsy results consistent with PBC Stage 4 (Ludwig 1978)
- TE 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)

Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A, Section 7.3, Table 3 and Table 4).

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

9.7.3.2. Progression to Cirrhosis

When a subject identified as noncirrhotic at Baseline per the criteria listed in Section 9.7.3.1 exhibits any signs or symptoms associated with progression to cirrhosis, as defined by the same criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy (centrally read) unless not medically indicated. Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis.

Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.

Sites participating in the paired biopsy substudy must confirm progression to cirrhosis by biopsy as per the information outlined in protocol Addendum 2.

All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.

9.7.4. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors

outlined in Table 6 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 Child-Pugh 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. It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen.

Table 6: 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)

9.7.5. Mayo Risk Score

Mayo Risk Score (MRS) (Dickson 1989) is calculated and reported within the EDC system based on data entered into the eCRF. Calculation of MRS includes investigator assessment of peripheral edema and the use of diuretic therapy, which will be assessed during adverse event and concomitant medicine review at the scheduled visits and entered into the eCRF, as well as total bilirubin, albumin, and prothrombin time results obtained from the central laboratory data.

9.7.6. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 week to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 3 weeks to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 week to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample

was collected. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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.

Collection of 2 serum chemistry samples (collected at least 2 weeks apart) during Screening is required for confirmation of the pretreatment serum chemistry values, including the ALP and total bilirubin used to determine eligibility:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤5x ULN and/or an ALP >3x ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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
- Assess for the presence/absence of cirrhosis.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score
- Perform assessment for calculation of Mayo Risk Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.

- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.
- 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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.
- Assess and record any pretreatment-emergent AEs.
- Record current concomitant medications.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.
- In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (at all study sites where the device is available), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate. In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.

9.7.7. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).

- Perform TE at all study sites with access to Fibroscan® TE device. If TE has been done within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc), the procedure may be completed within the screening visit window, at Screening Visit 1 (if data is needed for cirrhosis assessment) or as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
- Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
- Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where the device is available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
  - Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- Review and record any nonstudy 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 subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- 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 tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF])
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Access the IWRS and dispense investigational product
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 1 Procedures

- Perform a physical examination.
- Assess and record AEs
- Review and record concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit laboratory requirements:
  - At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via

telephone at the Month 1 visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;

- If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Month 1 visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;
- A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- 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.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.

- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. 1-Month Post-Titration Visit Procedures

- Perform a physical examination.
- Assess and record AEs.
- Review and record concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration laboratory requirements:
  - At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;

  - A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 6 Procedures

- Perform a physical examination.
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.

- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.12. Month 9 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- 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.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.

- PK assessment in participating subjects at select study sites (see Section 9.7.13).
- In preparation for the DEXA bone density scan to be done at the Month 12 visit (at all study sites where the device is available), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.13. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule.

Following collection of the Month 9 fasted samples (refer to Section 9.7.12, subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of study medication and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the study medication (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4-hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink with no other food allowed until after the final 6-hour post-dose sample is collected. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.14. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).

- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires and (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Conduct a DEXA bone density scan (at all study sites, where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at all study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19

  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.15. Month 3 and Month 9 Continued Follow-Up Procedures (±2 weeks)

- Perform assessments for calculation of Child-Pugh Score.
- Assess and record AEs.
- Review and record concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.16. Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])

- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.6)
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- Review and record any nonstudy 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
  - Blood sample for future analysis (refer to Section 11.1.2.3).
- At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (at all study sites where the device is available), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.

- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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

9.7.17. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an endoscopy (at all study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record concomitant medications.
- Review and record any nonstudy 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.
- Verify that the subject has fasted for at least 8 hours.

  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
  - Blood sample for future analysis (refer to Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.18. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject

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 and EOS procedures in the CRF.

Table 7: 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 IP	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[c]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[c]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

[a] Refer to Section 7.1.2 Schedule of Study Procedures, Table 2 for all procedures and evaluations required at the End of Treatment and End of Study Visits.

[b] Includes initiation of commercially available OCA.

[c] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.8.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessment for calculation of Mayo Risk Score.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.6).
- Perform TE at all study sites with access to the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).
- Conduct a DEXA bone density scan (at all study sites where the device is available; not required at EOT/EOS if done within 6 months); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- Review and record any nonstudy 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 accountability, and review dosing diary with the subject; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.

  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Blood sample for future analysis (refer to Section 11.1.2.3)

9.7.19. 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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin is observed during the course of the study, refer to Section 8.4.1.1 to confirm whether an unscheduled safety visit is required.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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 trial sites in support of clinical study 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 Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)

- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- 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 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Individual components of the primary endpoint
- Liver-related death
- Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.
  - Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in Addendum 2).
- HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.
- Liver biochemistry (see Table 11 for list of analytes to be tested)
- Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ELF, and Fibroscan (and others as determined during the course of the study).
- Clinical outcomes, including individual component of the primary endpoint (where available), liver transplant, and death will be compared to historical controls.
- PK of OCA and its conjugates.
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any

endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Noninvasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other Secondary Assessments

- OCA (OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide) and C4 will be assayed to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
  - Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study.

IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

- Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Section 12.1.6 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 13.4) 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 suspected unexpected serious adverse reaction (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 13.4.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definitions of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject 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.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.2. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Relationship of Adverse Events to Liver Biopsy

The Investigator will document her/his opinion of the relationship of an AE to liver biopsy using the criteria outlined in Table 9.

Table 9: Relationship of Adverse Events to Liver Biopsy

Relationship	Description
Related	A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.
Not Related	Any event that does not meet the above criteria.

12.1.4. 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 CRF. 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 subject may experience slight discomfort.
2 = Moderate	Causing some limitation of usual activities; the subject may experience annoying discomfort.
3 = Severe	Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

12.1.5. Reporting of Adverse Events and Serious Adverse Events

12.1.5.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

12.1.5.2. 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 be reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521

If an SAE is reported by email 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:

- Subject 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 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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

The Investigator is responsible for submitting information on 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, 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 12.1.6.

12.1.6. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition qualify as SAEs (see Section 12.1.1.2). The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.5.2). 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.

Given that the liver-related clinical outcome events may also meet the criteria of a SUSAR, but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly, the Sponsor will not expeditiously report suspected liver-related 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 "study event" on the AE CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.

The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 or oesophageal varices haemorrhage), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological or clinical progression to cirrhosis (preferred term: hepatic cirrhosis).

12.1.7. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Medical Monitor, 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 subject 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.

12.1.8. 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 12.1.5.2.

SAEs that occur in subjects 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 12.1.5.2.

12.1.9. Notification of Poststudy 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 12.1.5.2.

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 12.1.5.2.

12.1.10. 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 subject 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 subject 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 CRF. 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 subjects 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 CRF.

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.

12.1.11. 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 sae@interceptpharma.com or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

The subject 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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 12.1.5 must also be followed.

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening Visit 1, Month 12, and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Dual Emission X-Ray Absorptiometry

A bone density assessment will be done using the DEXA scan.

12.2.6. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.7. Laboratory Assessments

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

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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, and the normal reference ranges for liver biochemistries are shown in Appendix C.

Table 11: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[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	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Blood Sample for Future Analysis	PBC autoantibodies and other cytokines and interleukins TBD
Other	OCA (parent and conjugates [glyco and tauro], OCA-glucuronide) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.11 through pregnancy outcome.

MELD scores, Child-Pugh score, and MRS will be calculated at screening, and at quarterly (MELD and Child-Pugh scores) or semi-annual (MRS) visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the first interim analysis, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK Population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8.

13.1.2. Determination of Sample Size

The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3× ULN. The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years of subject accrual and 6 years of follow up.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.
- A dropout rate of 10% is assumed

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

13.1.2.1. Sample Size Monitoring

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an

opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)

- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.10 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3). The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time-to-event secondary efficacy analyses will compare OCA versus placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Progression to cirrhosis
- Time to occurrence of HCC
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as baseline TE, where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic (See Section 9.7.3.1). Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.

For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2).

Analyses of changes in MELD score, Child-Pugh score, MRS, IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.5.1. Association of Biochemistry with Clinical Outcomes and Clinical Benefit

The association between biochemistry including ALP and bilirubin with clinical outcomes will be assessed and the clinical benefit of OCA using biochemistry as a surrogate endpoint will be evaluated. Detailed analysis will be described in the SAP.

Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA using biochemistry as a surrogate endpoint for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN (Corpechot 2008)

- ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67x ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76x ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, "where no obvious single optimal external control exists, it may be advisable to study multiple external controls". In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, which serves as an external control for supportive analysis.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is "similar" to a participating subject. The historical database control should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.3).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment between the treated subjects and the matched natural history subjects.

A full range of covariates across which the treatment and historical controls might differ will be considered to mitigate potential bias. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the

covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible. Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation, to avoid biased results that are in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.

A third-party statistician(s) will perform the propensity score modeling and matching. This third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses. Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, HCC, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)
- Time to liver transplant or liver-related death

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), using similar statistical methodology as specified above.

Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.

13.1.9. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below. In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.

13.1.9.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.9.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.9.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified time point for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.10. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive

and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however, hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.11. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. Subgroups will be assessed at Baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)

- Early (normal albumin and normal bilirubin)
- Moderate (abnormal albumin or abnormal bilirubin)
- Advanced (abnormal albumin and abnormal bilirubin)

The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.

- Monotherapy in patients who are intolerant or non-responsive to UDCA
- Elderly patients

Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.

Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.

13.1.12. Continuous Monitoring and Interim Analyses

Blinded safety reports including the accrual of events, drop outs, and/or loss of subjects to commercially available OCA will be reviewed by the DMC on a regular basis.

Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% (64 events) and 75% (96 events) of clinical outcome events, respectively.

The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

13.2.4. Cardiovascular Adjudication Committee

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).

13.3. 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 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 subjects. 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 subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (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 subject safety, which alter the conduct of this study. The Investigators will inform the subjects of such actions and the protocol, patient information sheet (PIS), and consent will be revised, as appropriate.

13.4. Adjudication Committees

All suspected liver-related clinical outcomes, 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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. 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.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 Medical Monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, 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 (when available) 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: The Sponsor, 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.

19. LIST OF REFERENCES

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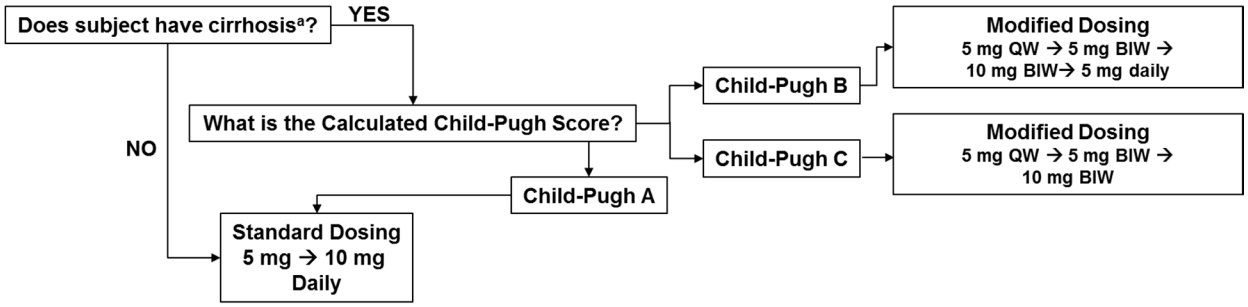
APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT

Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment

An overview of the modified dosing regimen for subjects with Child-Pugh Class B or Child-Pugh Class C is presented in Figure 2 and Table 12.

Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5 mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability and biochemical response. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly.

Figure 2: Dosing by Cirrhosis Status and Child-Pugh Score



[a] Cirrhosis may be assessed by histology or non-histological methods as defined in Section 9.7.3.
BIW = twice weekly; QW = once weekly

Table 12: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Modified Dosing Regimen	
	Child-Pugh B	**Child-Pugh C**
Starting Dose[a] (Day 0)	5 mg once weekly	5 mg once weekly
Titration 1[b] (≥Month 3)	5 mg twice weekly[c]	5 mg twice weekly[c]
Titration 2[b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]	10 mg twice weekly[c]
Titration 3[b] (≥6 weeks after Titration 2)	5 mg daily	NA

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

Modified Dosing Regimen for Subjects with Child-Pugh B Hepatic Impairment

Subjects with cirrhosis and classified as Child-Pugh B at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in Figure 2. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and

following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to twice weekly dosing with 10 mg OCA or matching placebo. Subjects with at least 6 weeks of twice weekly dosing at 10 mg OCA or matching placebo, and meeting dose titration criteria, should up-titrate to the maximum allowed dose of 5 mg OCA or matching placebo once daily.

Investigators may decrease the dosing frequency (back to once or twice weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Modified Dosing Regimen for Subjects with Child-Pugh C Hepatic Impairment

Subjects with cirrhosis and classified as Child-Pugh C at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in Figure 2. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score

Subjects on a modified dosing regimen who demonstrate a change in cirrhosis status and/or Child-Pugh Score should have their dose of investigational product modified to match their current status per the appropriate dosing regimen (see Section 7.4, Table 5); however, changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as changes in status. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change to the dosing regimen. Investigators may contact the Medical Monitor at any time to discuss potential changes to dosing.

Possible scenarios for dosing modifications include:

- Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C
- Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study
- Improvement in classification of Child-Pugh Score from C to B
- Improvement in classification of Child-Pugh Score from B to A; these subjects may be eligible to transition to the standard dosing regimen

Subjects may titrate dose and dosing frequency up or down as appropriate, within the appropriate dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month Post-Titration

Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.10).

Unscheduled Titration Visit, Optional Visit

An unscheduled up-titration visit may be scheduled for as early as 6 weeks after the initial titration visit (or subsequent titration visit) occurs for subjects who are following the modified dosing regimen. The visit procedures required for the unscheduled titration visit are outlined below. Subjects who up titrate at an unscheduled visit will continue to follow the regular visit schedule for all other study visits.

For subjects who up titrate at an unscheduled visit the following procedures will be performed:

- Assess and record AEs.
- Review and record concomitant medications.
- Perform the pre-Titration Tolerability Assessment as outlined in Section 7.4.1.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

For subjects who up titrate at an unscheduled visit: The + 1-week window week related to the 1-Month Post-Titration visit can be extended for up to an additional 5 weeks to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the window is extended past +1 week allowed visit window, at a minimum, a telephone safety contact should then be performed 1-month post-titration.

APPENDIX B. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

APPENDIX C. REFERENCE LABORATORY VALUES FROM CENTRAL LABORATORIES

Covance Central Laboratories (Indianapolis, Indiana, US [for North America and Latin America regions]; Geneva, Switzerland [for Europe]; and Singapore [for Asia-Pacific region]) will serve as the central labs for analysis or specimen management for the analytes listed in the Table 11 of Protocol 747-302 Version 4. The following in text table provides the Covance Laboratory reference ranges for the pertinent liver biochemistries analyzed by Covance. These reference ranges are sex and/or age specific, and can change during the course of the clinical trial; therefore, investigative sites should always refer to the reference ranges available on the Covance issued laboratory reports.

		Covance Indianapolis		Covance Geneva and Covance Singapore	
Analyte	Sex	Age[a]	Reference Range	Age[a]	Reference Range
Albumin	Both	18Y – 69Y	SI Units: 33-49 g/L Conventional Units: 3.3-4.9 g/dL	18Y – 69Y	33-49 g/L
		69Y-80Y	SI Units: 33-46 g/L Conventional Units: 3.3-4.6 g/dL	69Y-80Y	33-46 g/L
		80Y-150Y	SI Units: 30-46 g/L Conventional Units: 3.0-4.6 g/dL	80Y-150Y	30-46 g/L
ALP	Female	18Y - 50Y	31-106 U/L	18Y - 50Y	31-106 U/L
		50Y - 60Y	35-123 U/L	50Y - 60Y	35-123 U/L
		60Y - 70Y	35-123 U/L	60Y - 70Y	35-123 U/L
		70Y - 80Y	35-123 U/L	70Y - 80Y	35-123 U/L
		80Y - 90Y	35–135 U/L	80Y - 90Y	35–135 U/L
		90Y – 150Y	35-140 U/L	90Y – 150Y	35-140 U/L
ALP	Male	18Y - 50Y	31-129 U/L	18Y - 50Y	31-129 U/L
		50Y - 60Y	35-131 U/L	50Y - 60Y	35-131 U/L
		60Y - 70Y	35-125 U/L	60Y - 70Y	35-125 U/L

		Covance Indianapolis		Covance Geneva and Covance Singapore	
Analyte	Sex	Age[a]	Reference Range	Age[a]	Reference Range
		70Y - 80Y	35-130 U/L	70Y - 80Y	35-130 U/L
		80Y - 90Y	35–125 U/L	80Y - 90Y	35–125 U/L
		90Y – 150Y	35-125 U/L	90Y – 150Y	35-125 U/L
ALT	Female	18Y – 69Y	6-34 U/L	18Y – 69Y	6-34 U/L
		69Y – 150Y	6-32 U/L	69Y – 150Y	6-32 U/L
ALT	Male	18Y – 69Y	6-43 U/L	18Y – 69Y	6-43 U/L
		69Y – 150Y	6-35 U/L	69Y – 150Y	6-35 U/L
AST	Female	18Y – 59Y	9-34 U/L	18Y – 59Y	9-34 U/L
		59Y – 150Y	9-34 U/L	59Y – 150Y	9-34 U/L
AST	Male	18Y – 59Y	11-36 U/L	18Y – 59Y	11-36 U/L
		59Y – 150Y	11-36 U/L	59Y – 150Y	11-36 U/L
Direct Bilirubin	Both	18Y – 150Y	SI Units: 2-7 umol/L Conventional Units: 0.1-0.4 mg/dL	18Y – 150Y	2-7 umol/L
Indirect Bilirubin	Both	0Y – 150Y	SI Units: 0-21 umol/L Conventional Units: 0.0-1.2 mg/dL	0Y – 150Y	0-21 umol/L
Total Bilirubin	Both	18Y – 150Y	SI Units: 3-21 umol/L Conventional Units: 0.2-1.2 mg/dL	18Y – 150Y	3-21 umol/L

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Y = years; SI=International System of Units
[a] The unstated word "to" is implied by the "dash" appearing in age specific reference ranges. A range such as "0-59 years" and "59-150 years" means: "0 up to but not including 59 years" and "59 up to but not including 150 years".
Source: Covance Laboratory Services Manual Version 5.0.0. Dates vary by region: 10 Nov 2016 (North America), 22 Nov 2016 (Europe and Singapore)

APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

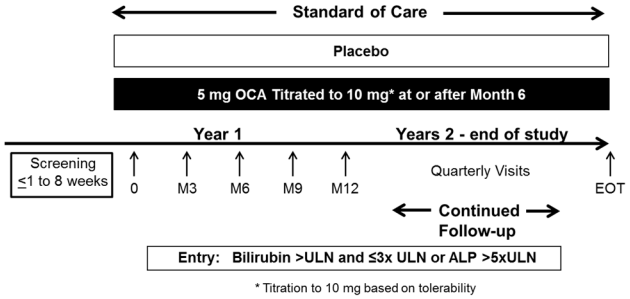
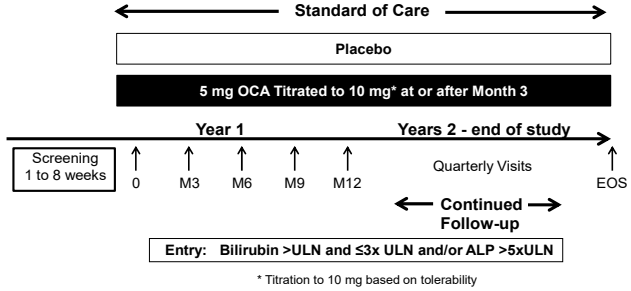
Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: 29 April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact: PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone: PPD **(Pacific time zone)** Mobile: PPD Email: PPD	Contact: PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone: PPD **(Pacific time zone)** Mobile: PPD Email: PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP)	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP)

Section	Original Text	Revised Text
	and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Section	Original Text	Revised Text
Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5×ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and/**or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12.	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>3. Mean total bilirubin >3× ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
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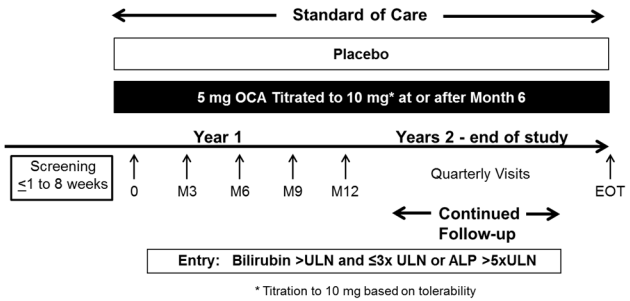
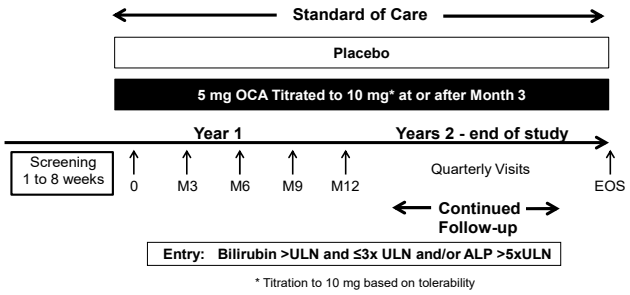
<tr><td>Synopsis</td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td>Statistical Methods: Other Efficacy Analyses
• Added text</td><td>Statistical Methods: Other Efficacy Analyses
• Development of varix/varices</td></tr>
<tr><td>4</td><td>List of Abbreviations
Added text</td><td>List of Abbreviations<table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC.</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment.</td></tr>
</table>

Section	Original Text	Revised Text
	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 **up to 4 years.** The **LSTE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete	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**.** The **LTSE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete
5.5.2.1	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.

Section	Original Text	Revised Text
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.**
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….

Section	Original Text	Revised Text
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)*** ***Visit Window ≤1 to 8 wks …*** ***Visit window in 2nd column added new text*** ***Added text*** *Footnote a:* All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on**	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now **"Screening Visit 1"*** *2nd column now **Screening Visit 2*** ***3** to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3*** *Footnote a* All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both**

Section	Original Text	Revised Text
	ALP (ALP >5× ULN), the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3× ULN).**	**analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**.
	Footnote b: The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed	*Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(± 1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.
	Footnote e: Medical history at Screening will smoking and alcohol consumption history and current habits for both.	*Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both.
	Footnote g: **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1)	*Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6)
	Footnote h: Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.	*Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote i: ***Added text***	*Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote j: ***Added text***	*Footnote j*: **Ultrasound will be conducted to enhanced HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	*Footnote k***:** ***Added text***	*Footnote k:* **Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central**

Section	Original Text	Revised Text
		laboratory evaluations per the Child-Pugh scoring system noted in the case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
	Footnote l: ***Added text***	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
	Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change	***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***
7.3	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched

Section	Original Text	Revised Text
	placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5× ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and**/or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile),

Section	Original Text	Revised Text
	contraception during the study and for 30 days after the end of treatment visit.	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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** 4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3× ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**

Section	Original Text	Revised Text
	5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	**5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent. The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text***	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures)**. The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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 potential adjudicated hepatic and/or cardiovascular events**

Section	Original Text	Revised Text
	The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	Concomitant Medications 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 CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to**

Section	Original Text	Revised Text
		continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.
9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for**

Section	Original Text	Revised Text
		the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding. **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.**
9.6	Restrictions **No additional restrictions.**	Restrictions **Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment
</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
<tr><td>EOS
(When subject terminates the study)</td><td>The final study visit; EOS will occur concurrent with EOT if a subject discontinues study medication at the time the subject’s</td></tr>
</table>
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Section	Original Text	Revised Text
		participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues study medication but continues in the study. EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**.	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart

Section	Original Text	Revised Text
	• For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).	• For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of **all available (at least 2; including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs**

Section	Original Text	Revised Text
		• **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours** – **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits** • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the**

Section	Original Text	Revised Text
		screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.
	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should**

Section	Original Text	Revised Text
		also be performed when platelet counts are <150 × 10^9 /L.
	• *Added text*	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• *Added text*	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• *Added text*	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**

Section	Original Text	Revised Text
9.7.6	Month 3 Procedures • ***Added text*** • ***Added text***	Month 3 Procedures • **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:** – **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • ***Added text***	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • ***Added text***	Month 9 Procedures • **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**

Section	Original Text	Revised Text
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.12), subjects who are participating in the PK assessment will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water. Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments**

Section	Original Text	Revised Text
		○ **Presence/absence of peripheral edema** ○ **Presence (degree)/absence of ascites** ○ **Presence (degree)/absence of hepatic encephalopathy**
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**

Section	Original Text	Revised Text
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will

Section	Original Text	Revised Text
		only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.**
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
		[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7**.**
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.	Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing
	Prior to the EOT Visit:	Prior to the EOT/**EOS** Visit:
	During the EOT Visit:	During the EOT/**EOS** Visit
	• Subject questionnaires (see Section 12.2.6)	• Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)**
	• Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable	• Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
	• ***Added text***	• Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6)
	• ***Added text***	• Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months)
	• ***Added text***	• Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• ***Added text***	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline**

Section	Original Text	Revised Text
		(and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of

Section	Original Text	Revised Text
	• ***Added text***	outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:** **a. PBC-40: The PBC-40 (Jacoby 2005) 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.** **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).**

Section	Original Text	Revised Text
		c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
12.1.1.2	Serious Adverse Event • ***Added text***	Serious Adverse Event **Events <u>not</u> 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**

Section	Original Text	Revised Text
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Section	Original Text	Revised Text
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to Appendix C)** and the Sponsor's policies.
19	List of References • Added text	List of References **Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83.** **Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.** **Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629.** **Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.**
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 (DATED 12 NOV 2015)

Rationale

The changes to Amendment 1 of the protocol, detailed below, generated specifically for regulatory authority requests, include an additional exclusion criteria and changes to text precluding UDCA naïve subjects from entering the study and clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, thus answering questions raised by regulatory authorities.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1.1. (Note: Revised text in Amendment 1.1 is indicated in bold font, and the text deleted from Protocol Amendment 1 is crossed out in the table below. Minor formatting changes are not listed.)

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
Title Page	Original: 03 October 2014 Amendment 1: 29 APRIL 2015	Original: 03 October 2014 Amendment 1: 29 **April** 2015 **Amendment 1.1: 12 November 2015**
Study Personnel Contact Information	~~Mobile: PPD (Pacific time zone)~~ Telephone: PPD ~~Telephone~~ PPD	(deleted) Telephone: PPD (deleted)
Synopsis, Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
Synopsis, Statistical Methods: Sample Size Justification	• ~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)
8.3 Subject Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
9.2 Concomitant Medications	(insertion)	**The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile**

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
		of caffeine, a sensitive CYP1A2 substrate, 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.
12.1.4.2 Reporting of Serious Adverse Event	~~Mobile: PPD (Pacific time zone)~~ Telephone: +1 ~~858 964 1571~~	(deleted) Telephone: PPD
13.1.2 Determination of Sample Size	~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)

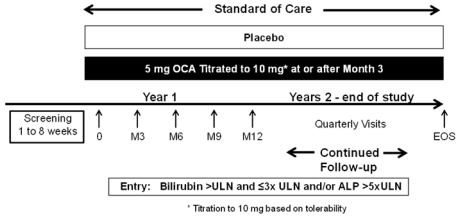
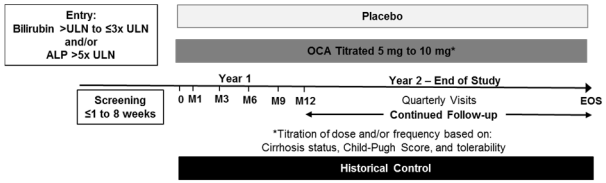
APPENDIX F. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 TO VERSION 3 (DATED 07 SEP 2016)

Rationale

The changes to Version 3 of the protocol, include dosing adjustments based on Child-Pugh scoring, additional exclusion criteria, changes to text precluding UDCA-naïve subjects from entering the study.

Please note that the Sponsor has renamed protocol "amendments" to "versions", therefore all future revisions that require a revised protocol will have an associated "version" number. The table below includes substantial revisions made to Protocol 747-302 under Version 3, which encompass the revisions captured in Protocol Amendment 1.1. Revised text in Version 3 is indicated in bold font, and the text deleted from Protocol Amendment 1.1 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 (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	... ~~Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups.~~ The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. ~~Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.~~	... Investigational product will be taken orally, once daily **for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C.** The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).	To incorporate a dosing and titration regimen based on subject's Child-Pugh Scores, to align with the recommended dosing regimen found in the Ocaliva US Package Insert for patients with hepatic impairment.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology. 7.1.1, Study Design Diagram, Figure 1	Schematic diagram 	Updated schematic diagram  **Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration**	Incorporate updated dosing scheme to reflect addition of Child-Pugh scoring.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	(insertion)	**Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:** • **Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.** • **For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.** • **Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability.** **Includes New Table: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Revised methodology to incorporate the changes in dosing for subjects based on the Child-Pugh Scores.
5.1, Overview	(insertion)	**The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication**.	Language updated as OCA is approved in the US with the trade name Ocaliva.

5.5.2.2, Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment	(Insertion)	**New section: Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment** **Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses and those from bile acids in the literature suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.** **Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose**	Provide the rationale to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores into the protocol.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		(full modified dosing regimen is described in Appendix A).	
5.6, Summary of Known Potential Risks with OCA	(Insertion)	**…These findings were seen more frequently with doses above 10 mg OCA. In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.**	Added two AE terms reported in the updated Investigator's Brochure.
7.1, Overall Study Design	…~~Investigational product will be initiated at 5 mg OCA or matched placebo.~~ Following 3 months of treatment with investigational product, ~~subjects~~ should be titrated ~~in a blinded manner (ie, subjects randomized to OCA will increase their dose to~~ 10 mg OCA) based on tolerability	Investigational product will be taken orally, once daily**. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo.** Following 3 months of **once daily** treatment with investigational product, **the dose** should be titrated **to a maximum** 10 mg OCA **or matching placebo once daily**, based on tolerability (see Section 7.3). **Subjects with cirrhosis and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.**	Amend the protocol to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores.
7.1.2, Table 1, Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2), 9.3, Treatment compliance	~~Safety Contact~~	This visit has been deleted.	Replaced with the 1 Month Post-Titration Visit.
	(Insertion)	Added the following visits: • Month 1 • 1 Month Post-Titration Visit	Visits were added to accommodate the updated dosing and titration regimen based on subject's Child-Pugh Scores.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	[b]~~The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 (± 1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.~~ [e]~~As soon as possible upon study discontinuation and as near as possible to last dose taken.~~ [n]~~Subject to begin dosing on Day 1~~	Deleted.	Result of table being updated for the dosing and titration regimen based on subject's Child-Pugh Scores.
	(Insertion)	Added the following study procedures: • Cirrhosis Status Assessment[e] • Assessments for Child-Pugh Scores[g] • Dose Titration: Standard Dosing[n,o] • Dose Titration: Modified Dosing [n,o] • Dosing Diary	Study procedures were added to accommodate the updated dosing/titration regimen. Dosing diary was added to improve compliance.

	(Insertion)	Added the following footnotes: • **[b]Safety Post-Titration visits must be performed 1 month + 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.** • **[c]Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.** • **[f]Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.** • **[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.** • **[n]Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.** • **[o]Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh score (Section 7.3). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for**	Added footnotes provide clarity regarding assessments and visits based on the evaluation of Child-Pugh scores.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A. • **[p]Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet**.	
7.1.2, Table 2, Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)		**New table- Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)**	Divided Schedule of Study Procedures into 2 tables, updated to include visits added per updated dosing/titration information.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.3, Planned Dosing Regimen	7.3 ~~Treatment Assignment~~ ~~Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3-month study visit or at any study visit thereafter depending on tolerability.~~	**7.3 Planned Dosing Regimen** Subjects will **be randomized to treatment with** either **OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.** **Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).** **For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.**	Section renamed to reflect changes in titration and dosing for subjects with hepatic impairment.
	(Insertion)	**New: Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Tables added to clarify changes in titration and dosing.
		New: Table 4: Determination of Dosing Regimen	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.4 Dose Titration Criteria	~~After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA~~ or ~~matched placebo (in a blinded manner) at the 3-month visit or any study visit following the 3 month visit based on~~ tolerability ~~of investigational product~~. ~~For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10 mg dose if tolerated~~	**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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh Score.** **Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.** **Tolerability Dose Titration - Investigators** may decrease **the dosing frequency** or dose **for any subject** at any time during the study, as considered **clinically** appropriate (eg, tolerability; **see Section 7.4.2).** **Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due** to **changes in cirrhosis or Child-Pugh 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.**	Entire section revised to reflect changes in titration and dosing.
7.4 Dose Titration Criteria	(Insertion)	**New: Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score**	

7.4 Dose Titration Criteria	(Insertion)	**Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).** **Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).** **Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.** **Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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 and table added to provide dosing guidelines to investigators.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.4.1, Pre-Titration Tolerability Assessment Requirements	(Insertion)	**7.4.1 Pre-Titration Assessment Requirements** **Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in study medication (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.** **To be eligible for a dose up-titration:** **• Subjects 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.** **• There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required**	Section added to provide guidance for assessing subject tolerability prior to titration.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
8.4.2, Other Reasons for Discontinuation of Study or Investigational Product	(Insertion)	• **Subject begins treatment with commercially available OCA** **… safety concerns and related to study drug** • Consent may be fully withdrawn **(in which case the subject discontinues both investigational product and study visits and procedures)** **…Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.**	Added text as Ocaliva is commercially available in the US and therefore subjects may be discontinued if they began off-study treatment with Ocaliva.
8.4.2.1, Elevated Liver Enzymes	(Insertion)	**New Section: 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.**	Section added to incorporate monitoring of liver test results during the study.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.1, Investigational Product Treatment Regimen	~~**9.1.1 Dose Adjustment Beginning at Month 3**~~ ~~After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted~~.	**At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.**	Section revised to reflect changes in titration and dosing.
9.2, Concomitant Medications	Subjects taking bile acid sequestrants (BAS) 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).	New sub-heading**:** ***Drug Interactions*** Subjects 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 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.** (…) **Information related to additional drug-drug interaction (DDI) studies is available in the current version of the Investigator's Brochure (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 with OCA that may be observed in study subjects.**	Section revised to provide additional information on drug-drug interactions with OCA.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.2.1, Prohibited Medications	… the Investigator should be cognizant of the possibility of double dosing ~~and encourage the discontinuation of open-label OCA therapy. However, if~~ commercial OCA therapy ~~remains, then investigational product should be discontinued to avoid potential double dosing~~. ~~Subjects that discontinue investigational product but continue commercial OCA therapy~~ are expected to continue through the end of the study, ~~and~~ the …	… the Investigator should be cognizant of the possibility of double dosing. **Subjects who continue with** commercial OCA therapy **must** discontinue **study medication and** are expected to continue through the end of the study. …	Ocaliva is commercially available in the US and, therefore, subjects wishing to take commercially available drug are not discouraged, but they must discontinue study medication.
9.7.1, Visit Windows	(insertion)	**Added the following visit windows:** • **Month 1 (+1 week [7 days])** • **Titration Visit – Standard Dosing Regimen (≥Month 3)** • **Titration Visit 1 – Modified Dosing Regimen (≥Month 3)** • **Titration Visit 2 – Modified Dosing Regimen (≥6 weeks after Titration Visit 1)** • **Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY) (≥6 weeks after Titration Visit 2)** • **Post-Titration Visit, (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency)**	Added visits to accommodate the updated dosing/titration scheme.

9.7.3, Assessing Cirrhosis	(Insertion)	**New: 9.7.3. Assessing Cirrhosis** **To determine which dosing regimen subjects should follow, the presence or absence of 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 is defined as a subject 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/mm3) with:** **– persistent decrease in serum albumin, or** **– elevation in prothrombin time /INR (not due to antithrombotic agent use), or** **– elevated bilirubin (2× ULN)** **Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A).** **Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in**	Added section to assess cirrhosis as this assessment will determine the acceptable dosing regimen based on a subject's Child-Pugh score.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		cirrhosis status will necessitate re-evaluation of the dosing regimen.	
9.7.4, Child-Pugh Score	(Insertion)	**9.7.4. Child-Pugh Score** **Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh 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.** **It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen**	Section added to provide Investigators with information on the Child-Pugh scoring system.
9.7.4, Child-Pugh Score	(Insertion)	**Table 6 (New) Child-Pugh Scoring System**	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.6, Screening Procedures (1 to 8 Weeks prior to Day 0)	(Insertion)	The following procedures were added: Screening Visit 1 procedures are as follows: • **Provide the subject with a dosing diary to document his or her dosing** • **Assess for the presence/absence of cirrhosis** • **Perform status assessment for calculation of Mayo Risk Score** Screening Visit 2 procedures are as follows: • **Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.**	Procedures added to assess cirrhosis.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.7, Day 0 Procedures (Randomization)	9.7.4. ~~Day 0 Procedures~~ ~~• Perform an ultrasound for hepatocellular carcinoma (HCC) surveillance (if equipment is unavailable, …~~ ~~• Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.~~ ~~` Presence/absence of peripheral edema~~ ~~` Presence (degree)/absence of ascites~~ ~~` Presence (degree)/absence of hepatic encephalopathy~~	9.7.**7**: Day 0 Procedures (Randomization) • **Provide the subject with a dosing diary to document his or her dosing.**	Updated visit to accommodate the updated dosing/titration scheme.
9.7.8, Month 1 Procedures	9.7.5 Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone])	9.7.**8** Month 1 Procedures • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:** **- At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, …** **- If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. …**	Revised section to include the new Month 1 visit procedures.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.9, Month 3 procedures, 9.7.11, Month 6 Procedures, 9.7.12, Month 9, 9.7.14, Month 12 Procedures	(Insertion)	• **Perform assessments for calculation of Child-Pugh Score**	Added procedure to accommodate the updated dosing/titration scheme.
9.7.9 thru 9.7.17	(Insertion)	**If up-titration will occur at this visit, complete the pre-titration visit and visit related assessments as outlined to ensure all procedures required for dose titration eligibility have been met, including the required review of the dose titration laboratory parameters.** • **Provide the subject with a dosing diary to document his or her dosing** • **… review dosing diary with the subject**	Text added to clarify procedures required before up-titration.

9.7.10, Post Titration Visit Procedures	(Insertion)	New**: 9.7.10. Post Titration Visit Procedures** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.** • **Obtain blood samples for serum chemistry, hematology, and coagulation tests.** • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration visit requirements:** **- At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.** **- If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review**	Added visit to accommodate the updated dosing/titration scheme.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		concomitant medications, and assess investigational product compliance. • **Schedule the next visit, reiterate dosing instructions, and advise the subject:** **- 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…**	
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	(Insertion)	**…Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule**.	Clarify that subjects with hepatic impairment may continue to participate in the PK assessment.
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink…	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink **with no other food allowed until after the final 6-hour post dose sample is collected…**	Clarify PK collection procedures.
11.1.2.2, Other Secondary Assessments	• OCA (~~and its conjugates~~) and C4 will be assayed	• OCA **(OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide)** and C4 will be assayed **to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified**.	Clarify the analytes to be measured for the PK analyses.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
11.1.2.4, Potential Clinical Outcome Events	(Insertion)	**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 13.4.**	Revised to clarify that potential clinical outcome events meeting the criteria of a SUSAR will not be reported to regulatory authorities expeditiously.

12.1.4.2 Reporting of Serious Adverse Event	In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the ~~medical monitor.~~ All SAEs ~~occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious)~~ must be reported to the ~~medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE~~. SAEs are reported by entering the SAE data into the ~~electronic data capture (EDC) system~~. Entering the SAE data into the EDC system will automatically notify the ~~medical monitor~~ of the event. In the event that the EDC system is inaccessible, an SAE may be reported by ~~telephone or fax~~ using a paper SAE Report form. 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: ~~subject~~ number and ~~initials, a description of the event~~, at least **one** criterion classifying the event as serious and the name and title of the reporting individual. ~~Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting~~ to regulatory authorities by the Sponsor or designee(s). ~~Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to~~	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 be reported by: • **E-mail to the SAE email address: sae@interceptpharma.com** • **Fax** using a paper SAE **report** form: **+1 800 497 8521** • **Telephone: +1 858 964 1571** 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: • **Subject** 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 Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) **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**	Updated guidance for reporting SAEs.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	~~+1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible~~. 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. ~~A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).~~ The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) ~~safety reports (SUSARs)~~ that occur during the study within the time frames required by each regulatory agency. ~~The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).~~ ~~Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities~~	**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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.** **The Investigator is responsible for submitting information on IND 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND 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 12.1.5.**	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Section 12.1.5, Suspected Liver-related Clinical Outcome Events	Clinical Outcome Events ~~(Appendix A) as well as Anticipated Events (Appendix B) will not undergo~~ expeditous reporting.	**12.1.5 Suspected Liver-Related Clinical Outcome Events** **Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.** **Given that the liver-related clinical outcome events could also meet the criteria of a SUSAR, please refer to Section 11.1.2.4.** **The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial and peritonitis (preferred term: peritonitis bacterial).**	Updated section to account for events related to hepatic impairment**.**

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
13.2.4, Cardiovascular Adjudication Committee	13.2.3 (…) In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study ~~and will be described separately~~.	**New Section: Cardiovascular Adjudication Committee** In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. **Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).**	Committee added to assess cardiovascular events in subjects during the study.

13.4, Adjudication Committee	All ~~potential endpoint events~~ will be reviewed by ~~an~~ adjudication committee before inclusion in the any analysis. The ~~adjudication of potential clinical endpoint~~ events will include, ~~but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership~~, the reporting of events by the study site, ~~reporting~~ of the ~~final assessment,~~ supply of source documentation to the committee, ~~the~~ review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members ~~will remain blinded to treatment group throughout the study~~. ~~In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.~~	All **suspected liver-related clinical outcomes, 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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific**	Committees added to assess liver impairment in subjects during the study.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.	
Appendix A, Modified Dosing Regimen for Subjects with Child-Pugh B/C Hepatic Impairment	(Insertion)	New**: APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT**	Added section to describe changes in dosing and titration for subjects assessed as cirrhotic Child-Pugh B or Child-Pugh C.
Appendix B, LIST OF STUDY 747-302 OUTCOME EVENTS	Was Appendix A	Now Appendix B	The hepatic dosing appendix became Appendix B
Appendix C	~~LIST OF STUDY 747-302 ANTICIPATED EVENTS~~	Deleted	Replaced by Appendix B, more comprehensive description of the outcome events.

APPENDIX G. SUMMARY OF CHANGES: PROTOCOL VERSION 3 TO PROTOCOL VERSION 3.1 (DATED 23 DEC 2016)

Please note that Protocol 747-302 Version 3.1 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. This summary of changes is provided for completeness. A full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided in Appendix I.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the expansion of the spectrum of stages of PBC disease, the addition of progression to cirrhosis as a secondary endpoint, and the addition of two interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

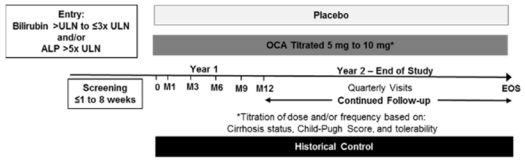
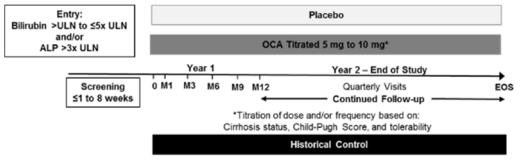
The following table includes revisions that were made to Protocol Version 3.1 with an associated reason or justification for the change. Rationales (Justifications for Change) that impact multiple sections are provided below and referenced in the table with the appropriate rationale number.

1. The phase of the study has been changed from '3b' to '4' to reflect that this is a post-marketing study.
2. The term 'primary biliary cirrhosis' has been changed to 'primary biliary cholangitis' throughout the document to reflect recent changes in nomenclature for PBC.
3. The increase in number of required events from 121 to 127 is due to the addition of two interim analyses (IA), which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy or futility) of the study. One IA will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). Inclusion of patients with earlier stage disease will also increase the time to event requiring more events in order to keep follow-up to approximately 6 years.
4. The first-year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by two years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.
5. 'Encephalopathy' has been modified to 'Hepatic Encephalopathy' to clarify that the relevant clinical outcome endpoint should be related to hepatic disease.

6. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of Hepatocellular Carcinoma.
7. **Broadening the Spectrum of Disease:** Lowering the minimum allowable baseline ALP to 3x ULN and raising the maximum allowable baseline total bilirubin to 5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the phase 3 protocol 747-301.
8. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
9. The increase in enrollment from 350 to 428 is due in part to the increased number of events, and in part due to the change in the estimated Placebo baseline hazard rate which resulted from changing the lower limit of ALP from 5× ULN to 3× ULN in the enrollment criteria #2.
10. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential non-invasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of 302.

The text deleted from Protocol Version 3 is crossed out while revised text in Version 3.1 is indicated in bold font in the table below. Minor/editorial changes and non-substantial changes are not listed individually in the summary table below.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	**Or if Not Available:** Contact: PPD **MD, PhD Medical Director, Clinical Research,** Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	Back-up medical monitor responsibilities were transferred to PPD
Synopsis, Studied Period (years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	~~3b~~	**4**	Rationale 1
Synopsis, Objectives, Primary, Statistical	• Encephalopathy (as defined by a West Haven score of ≥2) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5 Rationale 6

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis		• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities **unless confirmed by biopsy**	
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***Insertion*** To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects	**To assess the effect of OCA compared to placebo on progression to cirrhosis** To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 6
Synopsis, Methodology: Schematic Diagram Section 7.1.1 Study Design Diagram, Figure 1	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.	Rationale 7 Rationale 8

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (planned)	Approximately ~~350~~ subjects	Approximately **428** subjects	Rationale 9
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ≤~~3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 7
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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:	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below:	Standardizing language across protocols; removing double-barrier terminology

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 3.1, 23 December 2016)</th><th>Justification for Change</th></tr>
<tr><td></td><td>• ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~
• Intrauterine device (IUD)~~; 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 subject</td><td>• Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
• Intrauterine device (IUD)
• Vasectomy (partner)
• Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
• Abstinence, if in line with the preferred and usual lifestyle of the subject</td><td></td></tr>
<tr><td>Synopsis, Exclusion Criteria
Section 8.3 Subject Exclusion Criteria</td><td>3. Mean total bilirubin >~~3~~x ULN</td><td>Mean total bilirubin >**5**x ULN</td><td>Rationale 7</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Hepatic encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities already confirmed by biopsy</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td>Rationale 5

Rationale 10</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		Progression to cirrhosis — **Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated**	
Synopsis, Statistical Methods Analysis Populations	The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population.
Synopsis, Statistical Methods, Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints.	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints.	
Synopsis, Statistical Methods, Other Efficacy Analyses Section 13.1.5 Additional	***Insertion***	**Progression to cirrhosis will be assessed in the subset of subjects considered non-cirrhotic at baseline using available medical history, clinical, and laboratory assessments as well as baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be**	Rationale 10

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Secondary Efficacy Analyses		**considered non cirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the trial in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of non-cirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.** **Analyses for the histological assessment conducted as part of the biopsy sub-study are defined in Appendix C.**	
Synopsis, Statistical Methods, Safety Analyses	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will ~~compare OCA and placebo using~~ the Safety Population.	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will **be summarized by treatment group for** the Safety Population.	Clarification of summary analyses
Synopsis, Statistical Methods, Sample Size Justification	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up • ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **subject** accrual and 6 years of follow up • **Two interim analyses and one final analysis are planned** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	Rationale 4 Rationale 3
Section 5.6 Summary of Known Potential Risks with OCA	~~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).~~	**An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg and in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies.**	Language has been updated to reflect Sponsor standards

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	Insertion	**Refer to the IB for additional information regarding the known potential risks with the investigational product.**	
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3). The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5**× ULN or ALP >**3**× ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**….based on tolerability **and biochemical response** (see Section 7.3) The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 1 Rationale 9 Clarification Rationale 7 Rationale 3
Section 7.1.2 Schedule of Study Procedures, Table 1	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration** • **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	[j] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments at Day 0 and Month 12)
	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	[m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds**: unless HCC has already confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis. Rationale 8
	[o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. …	[p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. …	Clarification
	[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a baseline (e.g. Day 0) genetic sample is not obtained, subsequent genetic samples are not**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		required to be collected during the course of the study.	
Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions*** [i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~ Not required if done within ~~6~~ months of visit. ***Insertion*** (subsequent footnotes are renumbered accordingly) [j] Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up** [i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. Not required if done within **3** months of visit [j] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Not required if done within 6 months of visit.** [k] Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: **unless HCC has already been confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments) Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	are expected to have a minimum follow-up time of approximately 6 years.	are expected to have a minimum follow-up time of approximately 6 years.	
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study.	Rationale 9
Section 7.3 Planned Dosing Regimen	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score ***Footnotes were re-ordered*** [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin >ULN**. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Rationale 8
Section 7.4 Dose Titration Criteria	***Insertion***	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total**	Added language to clarify titrations (up or down)

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.	
Section 8.4.1.1 Severe Drug-Induced Liver Injury	***Insertion***	**If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. Subjects who develop significant drug-induced liver injury which is considered 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, evidence of 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.** **Severe drug induced-liver injury that is not considered related to investigational product must be discussed with the Sponsor before investigational product is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed**	Added guidelines for subjects who develop severe Drug-Induced Liver Injury

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time. **All suspected drug-related hepatic injury events will be adjudicated by the Hepatic Safety Committee (see Section 13.4).**	
Section 8.4.1.2 Liver Transplantation	***Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product***	**8.4.1.2 Liver Transplantation** **Subjects must discontinue investigational product after undergoing liver transplantation surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection.**	The relocation of this statement from within Section 8.4.2 to 8.4.1.2 clarifies directions to discontinue subjects who undergo a liver transplant from investigational product but not study visits
Section 8.4.2 Reasons for Mandatory Interruption of Investigational Product	***Insertion/Reorganization***	**8.4.2 Reasons for Mandatory Interruption of Investigational Product** **Prior to re-starting investigational product after a prolonged interruption, the subject must be re-consented and new baseline visit procedures must be performed if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.**	This clarifies what should be done when a subject experiences a prolonged interruption in investigational product such as in the event of pregnancy
Section 8.4.2.1 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product	**8.4.2.1 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product	Language simplified and aligned with Sponsor standards

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~	**immediately,** but should continue with the study visit schedule. **As described in Section 12.1.9** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.9). New baseline procedures should include pregnancy testing.**	
Section 8.4.3 Other Reasons for Discontinuation of Study of Investigational Product	8.4.2 Other Reasons for Discontinuation of Study of Investigational Product Subjects ~~that~~ discontinue investigational product are expected to continue in the study until the end of the study~~, and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ or at the discretion of the Sponsor. ~~If~~ a subject ~~reaches an event,~~ he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who ~~choose to~~ discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and~~	**8.4.3** Other Reasons for Discontinuation of Study of Investigational Product 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. **With the exception of liver transplant, if** a subject **experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor):	Discontinuation of investigational product language updated to clarify the process that is to be followed after discontinuation and instruct subjects to continue regular visit schedule.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~the study will only terminate~~ (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or cardiovascular events~~. ~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.~~	– 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), liver-related clinical outcomes, and drug-related hepatic injury events.** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** To determine which dosing regimen subjects should follow, the presence or absence of 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~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as non-cirrhotic at baseline per the criteria listed in Section 9.7.3.1 exhibits any of those same criteria (excluding biopsy results consistent with PBC Stage 4), the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites**	Provides detail around the assessment of Progression to Cirrhosis as a secondary endpoint

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		participating in the paired biopsy sub-study (see Appendix C**) must confirm progression to cirrhosis by biopsy. All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	
Section 9.7.6 Screening Procedures	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN).	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5**× ULN and/or an ALP >**3**× ULN).	Reflects new inclusion criteria
Section 9.7.7 Day 0 Procedures	• Perform transient elastography ~~(TE; at selected study sites, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Perform transient elastography **at all study sites with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	Clarifies use of TE and modifies the time during which an historic TE report remains valid
Section 9.7.8 Month 1 Procedures Section 9.7.10 Post-titration visit Procedures	***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:	• **Perform a physical examination.** – In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit **laboratory** requirements:	Physical examinations 1 month after initiating dosing with investigational product will enhance safety monitoring Returning to the site for monthly laboratory assessments can present a significant burden on subjects, thus alternatives are provided for collecting lab samples; with the addition of the physical exam as well the requirement for these exams is provided in the context of the alternatives for laboratory specimen collection

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion***	• **Perform a physical examination** • **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	TE assessment has been added as biannual assessment at all study sites with access to Fibroscan® TE device Hepatic ultrasound should be performed biannually per AASLD and EASL guidelines for subjects with PBC
Section 11.1.2 Secondary Assessments	***Insertion***	• **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.** • **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (see Appendix C)**	Rationale
Section 11.1.2.4 Potential Clinical Outcome Events	The events listed in ~~Appendix A~~ will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	The events listed in **Section 12.1.5** will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	Appendix referencing clinical outcomes events was removed due to redundancy
Section 12.1.4.2 Reporting of Serious Adverse Events	***Insertion***	**Redacted medical record source documentation will be requested for all SAEs and emergency room visits.**	Added sentence regarding redacted medical records to align with Sponsor safety standards
Section 12.1.5 Suspected Liver-Related Clinical Outcome Events	~~For~~ liver-related clinical outcome events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, ~~please refer to Section 11.1.2.4.~~	**Given that the** liver-related 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 liver-related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes**	Updated to align with modified standard safety procedures and Sponsor standard language

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), and spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).	**endpoint. These events will be selected as a "study event" on the Adverse Event CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.** The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).**	
Section 12.1.7 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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours).	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 12.1.4.2.	Updated to align with modified safety procedures and Sponsor standard language
Section 12.1.8 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. Note that longer follow-up can sometimes reveal an off-drug repetition**	Updated to align with modified standard safety procedures and Sponsor standard language

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.	
Section 12.1.9 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~~ investigational product and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing~~ or ~~emailing~~ to ~~the Sponsor at~~ +1 800 497 8521 or sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use of investigational product.~~ The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see~~ Section 8.4.1~~).~~	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 8.4.2.1) 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** sae@interceptpharma.com **or faxed to** +1 800 497 8521. **The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.** The subject may **re-start** 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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**	Updated to align with modified standard safety procedures and Sponsor standard language

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 3.1, 23 December 2016)</th><th>Justification for Change</th></tr>
<tr><td></td><td></td><td>reporting procedures described in Section 12.1.4 must also be followed.</td><td></td></tr>
<tr><td>Table 10 List of Laboratory Analytes</td><td><table><tr><td>~~Measurement of Liver Fibrosis~~</td><td>~~Fibroscan~~</td></tr><tr><td>~~Bone Density Assessment~~</td><td>~~DEXA~~</td></tr><tr><td>Other</td><td>Insertion</td></tr></table></td><td>Deletion<table><tr><td>Other</td><td>OCA-glucuronide</td></tr></table></td><td>Measurements of liver fibrosis are captured in a different section

OCA-glucuronide was listed in the text but missing from the table</td></tr>
<tr><td>Section 13.1.1 Analysis Populations</td><td>• ~~The Randomized Population will include all randomized subjects~~</td><td>Deletion</td><td></td></tr>
<tr><td>Section 13.1.2.1 Sample Size Monitoring</td><td>9.1.2.1 Sample Size~~ Re-Estimation Plan~~
~~Therefore, starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups.
~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative~~</td><td>9.1.2.1 Sample Size Monitoring
Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups.
Deletion</td><td></td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~primary efficacy analysis is specified is Section 13.1.9.~~ ~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~		
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between the effect of OCA on ALP and bilirubin and the clinical benefit of OCA will be evaluated by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This analysis will be based on the ITT population.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
13.1.8 Supportive Analysis	***Insertion***	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1), using**	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		similar statistical methodology as specified above. **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	Sponsor has received agreement from regulatory authorities.
Section 13.1.9 Alternative Primary Analysis	~~13.1.9 Alternative Primary Analysis~~ ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section **13.1.2.1**). Similar statistical methodology as specified above in Section **13.1.8** for supportive analyses will be utilized.~~ ~~The propensity score quintile will be then be used as the stratification factor in the stratified log-rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section **13.1.8** will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~	***Deletion***	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the Sponsor has received agreement from regulatory authorities

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs and/or loss of patients to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy or futility) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.**	Explanation of the type of review that will be ongoing by the DMC during study conduct.
Section 19 List of References	***Insertion***	**Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential**	Additional relevant references were added.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.	
Appendix B List of Study 747-302 Outcome Events	~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~	**Deleted**	Redundant; Information is contained within the protocol
Appendix C Biopsy Sub-Study of Protocol 747.302: A Phase 4, Double-Blind, Randomized, Placebo-Controlled,	***Insertion***	**See Appendix C**	The purpose of this sub-study is to assess the effect of OCA versus placebo on the histological severity of disease (fibrosis/cirrhosis) in subjects with PBC. In addition, this sub-study will demonstrate the relationship between

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in subjects with Primary Biliary Cholangitis			histological changes and clinical, laboratory, and non-invasive measures indicative of progression to cirrhosis in patients with PBC.

APPENDIX H. SUMMARY OF CHANGES: PROTOCOL VERSION 3.1 TO PROTOCOL VERSION 4 (DATED 10 MAY 2017)

Please note that Protocol 747-302 Version 3.1 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. A full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided in Appendix I.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 Version 3.1 include:

- Hepatocellular carcinoma (HCC) has been redefined as a secondary endpoint;
- Following the broadening of the spectrum of disease, a commitment to enroll a minimum of 30% of subjects with abnormal bilirubin has been added to the protocol;
- Clarifications have been incorporated throughout the protocol based on the addition of a biopsy substudy in Addendum 2;
- Statistical language has been modified and added to clarify statistical assumptions and analyses including the addition of a Per Protocol (PP) Population;
- Background rationale has been updated to reflect the current approval status of Ocaliva; and
- Safety language has been updated throughout the protocol to reflect the updating of Sponsor standards.

Minor revisions include editorial changes such as removal of hyphens and capitalization of words. Minor revisions may be included in the following table when they are also part of major revisions; however, most minor/editorial changes and nonsubstantial changes are not listed individually.

The text deleted from Protocol Version 3.1 is crossed out while revised text in Version 4 is indicated in bold font in the table below.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Study Personnel Contact Information	~~**Or if Not Available:**~~ ~~Contact:~~ PPD ~~MD, PhD Medical Director, Clinical Research,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~Mobile:~~ PPD ~~(Pacific time zone)~~ ~~Email:~~ PPD PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD PPD ~~Clinical Operations,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~(Pacific time zone)~~ ~~Mobile:~~ ~~Fax:~~ PPD ~~Email:~~ PPD PPD		Updating emergency medical monitor contact information. The contact information for clinical operations and project management personnel is no longer required in the protocol per Sponsor's procedures.
Synopsis, Objectives, Primary, Statistical Methods – Efficacy Analyses	To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary ~~cirrhosis~~ (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:	To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary **cholangitis** (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:	Editorial correction HCC has been redefined as a secondary endpoint instead of a component of the primary

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy~~		composite-event endpoint per Regulatory Authority request.
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***In Section 6.2*** To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above ~~and also to include liver related death~~. To ~~characterize~~ the effect of OCA compared to placebo on progression to cirrhosis. To ~~assess~~ the PK of OCA and its conjugates in a subset of subjects.	**To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).** To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above. **To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.** To **assess** the effect of OCA compared to placebo on progression to cirrhosis. To **characterize** the PK of OCA and its conjugates in a subset of subjects.	HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request. Editorial change Editorial change Editorial change
Synopsis, Methodology Section 7.1, Overall Study Design.		**A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.**	To ensure enrollment of an adequate number of subjects with abnormal total bilirubin.

<table>
<tr><th>Section</th><th>Original Text
(Amendment 3.1, 21 December 2016)</th><th>Revised Text
(Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td>Section 7.1.1
Study Design Diagram,
Fig 1 (Footnote)</td><td>Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response.</td><td>Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN).</td><td>Clarification of biochemical response</td></tr>
<tr><td>Synopsis, Number of Subjects (Planned)

Section 7.2
Number of Subjects</td><td>Insertion in both, Synopsis and Section 7.2

Change in Synopsis section

Approximately 428 subjects</td><td>In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

Approximately 428 subjects are planned to be enrolled in the study.</td><td>Language added to allow for continued enrollment into the biopsy substudy; additional subjects are not anticipated to prolong the duration of the study.</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td></td><td>• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy.~~</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td></td><td></td></tr><tr><td>Secondary Objectives</td><td></td></tr><tr><td>HCC</td><td>Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy</td></tr></table></td><td>HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.</td></tr>
<tr><td>Synopsis, Statistical Methods

Analysis Populations</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBC Historical Control.</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP), Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBC Historical Control.</td><td>The randomized population is included within the Safety population.

The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.</td></tr>
</table>

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Primary Efficacy Endpoint Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	~~• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~ ***Section 13.1.3*** ~~• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy~~ The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	***Section 13.1.3*** The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request. Editorial change
Synopsis, Statistical Methods, Primary Efficacy Analysis Section 13.1.3 Primary Efficacy Analysis	***Insertion***	**The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses Section 13.1.4 Secondary Efficacy Analysis	***Insertion*** ***Section 13.1.4*** The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in the ITT population with respect to the key secondary efficacy endpoints.	**The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.** ***Section 13.1.4*** The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints.	The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints. Editorial change

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Additional Secondary Efficacy Analyses	~~Other~~ Efficacy Analyses The following secondary efficacy analyses will compare OCA ~~to~~ placebo ~~on time to the following events~~: • Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above) • Development of varix/varices • Liver-related death • Liver-related death or liver transplant Liver-related death, liver transplant, or MELD score ≥15	**Additional Secondary** Efficacy Analyses The following **time-to-event** secondary efficacy analyses will compare OCA versus placebo using **the ITT population**: • **Time to e**ach component of the primary efficacy endpoint (except MELD score ≥15 which is listed above) • **Time to d**evelopment of varix/varices • **Progression to cirrhosis** • **Time to occurrence of HCC** • **Time to l**iver-related death • **Time to l**iver-related death or liver transplant **Time to l**iver-related death or liver transplant, or MELD score ≥15	Editorial Change Progression to cirrhosis added as secondary endpoint in Version 3.1. HCC has been redefined as a secondary endpoint instead of a component of the primary composite event endpoint per Regulatory Authority request.
Synopsis, Statistical Methods, Additional Secondary Efficacy Analyses Section 13.1.5 Additional Secondary Efficacy Analyses	***Insertion*** Analyses for the histological assessment conducted as part of the biopsy substudy are defined in ~~Appendix C~~.	**For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy.** Analyses for the histological assessment conducted as part of the biopsy substudy are defined in **Addendum 2.**	Provides further details of progression to cirrhosis as outlined in the biopsy substudy defined in Addendum 2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	***Insertion*** The following assumptions were used in sample size calculations: • Two interim analyses and one final analysis are planned. ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to ~~clinical~~ outcomes.	**The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN.** The following assumptions were used in sample size calculations: • Two interim analyses and one final analysis are planned. **The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.** • **A dropout rate of 10% is assumed.** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to **liver-related** outcomes**, including all-cause mortality**.	Incorporation of the broadened spectrum of disease into the sample size justification. Clarification of interim analyses. Clarification of the assumed dropout rate. Clarification of outcomes being assessed in power calculations.
Section 5.1 Overview of PBC and OCA	5.1. Overview of Primary Biliary ~~Cirrhosis~~ and Obeticholic Acid Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis~~)~~ 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	5.1. Overview of Primary Biliary **Cholangitis** and Obeticholic Acid 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	Updating language to include accelerated and conditional approvals of OCA in the US and EU.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	necessitates liver transplantation or results in death. Ursodeoxycholic acid (UDCA), a physiological constituent of human ~~bile , is currently the only treatment approved for PBC~~ (Lindor 2009). While UDCA therapy ~~has~~ a marked effect on the treatment of PBC, up to 50% of patients ~~show~~ a suboptimal response or no response to UDCA. Such patients ~~are~~ at significantly increased risk of a poor clinical outcome due to PBC disease progression~~. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]).~~ Obeticholic acid (OCA) ~~is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.~~ ~~OCA is a modified bile acid and~~ farnesoid X receptor (FXR) agonist ~~that is~~ derived from the primary human bile acid chenodeoxycholic acid (CDCA~~). OCA is currently being developed in the United States (~~US~~) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States~~ Food and Drug Administration	necessitates liver transplantation or results in death. **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**), 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 (Pellicciari 2002). 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.	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	(FDA) ~~has~~ granted accelerated approval for Ocaliva ~~for the treatment of PBC.~~ Ocaliva ~~is not yet approved outside the United States for use in any~~ indication.		
Section 5.4 Overview of PBC and OCA	As of 31 Jan ~~2016~~, approximately ~~1726~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ subjects had PBC, ~~330~~ subjects had NASH, 41 subjects had diabetes mellitus/~~non-alcoholic~~ fatty liver disease ~~(NAFLD)~~, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~20~~ subjects had primary sclerosing cholangitis (~~PSC~~).	As of 31 Jan **2017**, approximately **2186** subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** subjects had PBC, **686** subjects had NASH, 41 subjects had diabetes mellitus/**nonalcoholic** fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **52** subjects had primary sclerosing cholangitis, **and 5 subjects had biliary atresia.** **----------** **[1]Includes estimated numbers from ongoing blinded studies.**	Language updated to include data from current IB.
Section 5.5.2.1 Rationale for OCA Dose	The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; ***Insertion*** Based on these data, ~~the indicated commercial doses of~~ OCA for the treatment of patients with PBC are 5 mg and 10 mg. ~~As such,~~ Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.	The Phase 3 PBC study **(Study 747-301)** subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; **Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus.** Based on these data, the **approved dosing regimens for** OCA for the treatment of patients with PBC are 5 mg and 10 mg. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose **for at least 3 months**, increasing to 10 mg OCA, if tolerated.	Provides rationale for the dosing in alignment with commercial labeling.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 5.6 Summary of Known Potential Risks with OCA	~~An increase in liver enzymes and~~ hepatic ~~AEs, including jaundice,~~ were observed in ~~subjects with liver disease at OCA doses between 10 mg and 50 mg and in~~ healthy ~~subjects who were~~ treated ~~at doses ≥100 mg in Phase 1,~~ multiple-~~dose studies~~. These findings were seen more frequently with doses ~~above~~ 10 mg OCA.	**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)**. 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).**	Language has been updated to reflect Sponsor standards.
Section 7.1.2 Schedule of Study Procedures, Table 1	[a] All subjects will have the chemistry panel retested to ensure subjects have two ALP and bilirubin assessments 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. [l] Endoscopy will be conducted at ~~selected~~ study sites where the device is available. [m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met~~.	[a] All subjects will have the chemistry panel retested to ensure subjects have **at least** two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. **Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility.** [l] Endoscopy will be conducted at **all** study sites where the device is available**.** [m] 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**.	Editorial changes
Section 7.1.2 Schedule of Study Procedures, Table 2	[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. ~~Not required if done within 3 months of visit.~~	[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available.	Editorial changes

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. ~~Not required if done within 6 months of visit~~. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met.~~	[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, postday 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm **suspected HCC**.	
Section 7.4 Dose Titration Criteria	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.	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, **biochemical response**, and clinical judgment. **Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).**	Editorial changes
Section 7.4.1 Pre-Titration Tolerability Assessment Requirements	• There must be no clinically significant increase (as determined by the ~~i~~nvestigator) in the subject's liver function tests. ~~Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19 should be implemented, as required.~~	• There must be no clinically significant increase (as determined by the **I**nvestigator) in the subject's liver function tests.	Clarification
Section 7.4.2	***The text in this section is moved to Section 8.4.***		To avoid redundancy

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Safety Criteria for Adjustment or Stopping Doses			
Section 8.4 Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	**[*Moved from Section 7.4.2 of Version 3*]** Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be **adjusted back** to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved. Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an **outcome** event, he or she should continue the regular visit schedule and continue taking investigational product as long as the **subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the** Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Clarification
Section 8.4.1.1 Reasons for Additional Monitoring Related to Liver Chemistries	***Modification of 8.4.3.1 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~~	**Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total**	Clarified guidelines for subjects who develop elevations in liver chemistries. Language related to interruption of investigational product is now located in Section 8.4.1.2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~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.~~	**bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored.**	
Section 8.4.1.2 Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	***Insertion***	**Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3x baseline (and >ULN)** • **Total bilirubin >2x 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 AE information should also be collected and the subject 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**	Clarified guidelines for subjects who develop elevations in liver chemistries.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		medications should be identified and discontinued if advisable. **If symptoms persist or repeat testing shows AST or ALT >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 study medication and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject 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**	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		be evaluated for drug-induced liver injury as provided in the guidelines below. **If at any time a subject 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.** Subjects who develop **evidence of severe** drug-induced liver injury, which 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. **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 subjects 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 subject to continue**	

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	Section 8.4.1.1: Subjects who develop ~~significant~~ drug-induced liver injury which is ~~considered~~ 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, ~~evidence of~~ functional hepatic impairment as indicated by rising bilirubin or INR that cannot be explained by progression of disease. ***Insertion***	**treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.** **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 13.4).**	
Section 8.4.1.3 Pregnancy	**8.4.2.1 Pregnancy** As described in Section ~~12.1.9~~ pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 ~~12.1.9~~). ~~New baseline procedures should include pregnancy testing~~.	**8.4.1.3 Pregnancy** As described in Section **12.1.11** pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 **12.1.11**.	Revised section number.
Section 8.4.2.1 Liver Transplantation	**8.4.1.2 Liver Transplantation** Subjects must discontinue investigational product ~~after undergoing liver transplantation surgery.~~ Subjects should be encouraged to ~~continue study visits, despite stopping investigational product, for continued study data collection~~.	**8.4.2.1 Liver Transplantation** Subjects **who undergo a liver transplant during the course of the study** must discontinue investigational product **and discontinue the study visit schedule. However, these** subjects 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**.	Clarification on process for subjects who undergo a liver transplant.

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Section 8.4.3 Other Reasons for Discontinuation of Study or Investigational Product	~~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. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18).~~ – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess suspected major adverse cardiovascular events (MAC), liver-related clinical outcomes~~, and drug-related hepatic injury events~~.	– Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess suspected major adverse cardiovascular events (MACE) **and** liver-related clinical outcomes. – **Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.18).**	Clarification of process
Section 9.7.1 Visit Windows	Screening |	Screening | **See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.**	
Section 9.7.3.2 Progression to Cirrhosis	When a subject identified as ~~non-cirrhotic~~ at Baseline per the criteria listed in Section 9.7.3.1 exhibits any ~~of those~~ same criteria ~~(excluding biopsy results consistent with PBC Stage 4)~~, the	When a subject identified as **noncirrhotic** at Baseline per the criteria listed in Section 9.7.3.1 exhibits any **signs or symptoms associated with progression to cirrhosis, as defined by the** same	Details the assessment of progression to cirrhosis.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites participating in the paired biopsy ~~sub-study (see Appendix C)~~ must confirm progression to cirrhosis by biopsy.	criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy **(centrally read)** unless not medically indicated. **Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis.** **Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.** Sites participating in the paired biopsy **substudy** must confirm progression to cirrhosis by biopsy **as per the information outlined in protocol Addendum 2.**	
Section 9.7.6 Screening Procedures	~~Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated~~ serum chemistry samples (at least 2 weeks apart) ~~to confirm~~ pretreatment ALP and total bilirubin ~~values~~: ***Insertion***	**Collection of 2 s**erum chemistry samples (**collected** at least 2 weeks apart**) during Screening is required for confirmation of the** pretreatment **serum chemistry values, including the** ALP and total bilirubin **used to determine eligibility**: • **When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Allows repeat assessments when baseline laboratory values are discrepant between Screening Visit 1 and Screening Visit 2.

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	• …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (~~selected~~ study sites ~~only~~), ***Insertion***	• …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 **(at all** study sites **where the device is available**), **In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.**	
Section 9.7.8 Month 1 Procedures Section 9.7.10 1-Month Post-Titration visit Procedures	***Insertion (9.7.8)*** ***Insertion (9.7.10)***	− **A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed**. − **A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed**.	Clarification
Section 9.7.12 Month 9 Procedures Section 9.7.14 Month 12 Procedures Section 9.7.16 Month 16 Continued Follow-Up Procedures Section 9.7.17 Month 12 Follow-up Procedures Section 9.7.18 EOS/EOT	***Section 9.7.12, 9.7.14, 9.7.16, 9.7.17, and 9.7.18*** *…DEXA procedure to be done at* ~~selected~~ study sites ~~only~~, ***Section 9.7.14, and 9.7.17*** • Perform an endoscopy (at ~~selected~~ study sites, where available)	***Section 9.7.12, 9.7.14, 9.7.16, 9.7.17, and 9.7.18*** *…DEXA procedure to be done at* **all** study sites **where the device is available** ***Section 9.7.14, and 9.7.17*** • *Perform an endoscopy (at **all** study sites, where **device is** available)*	Clarification

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 9.7.18 EOS/EOT	If the subject reports having eaten within 8 hours, document accordingly in the source and CRF ~~and remind the subject that fasting is required prior to all study visits~~.	If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.	Clarification
Section 10.3 Investigational Product Storage	~~The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical study 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.**	Updating temperature excursions language per Sponsor stability studies.
Section 11.1.2 Secondary Assessments	***Insertion*** • Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in ~~Appendix C~~). • Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c reactive protein (CRP), tumor necrosis factor α (TNF-α), FGF 19, cytokeratin-18 (CK-18) and ELF, (and others as determined during the course of the study).	• **Individual components of the primary endpoint.** • Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in **Addendum 2**). • **HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.** • Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c reactive protein (CRP), tumor necrosis factor α (TNF-α), FGF 19, cytokeratin-18 (CK-18) ELF, and **Fibroscan** (and others as determined during the course of the study). • **Clinical outcomes, including individual component of the primary endpoint**	Clarified and re-ordered bullets for consistency throughout document. Addition of Addendum 2. Reflects addition of a biopsy substudy available to interested sites in Addendum 2.

<table>
<tr><th>Section</th><th>Original Text
(Amendment 3.1, 21 December 2016)</th><th>Revised Text
(Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td>• Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.</td><td>(where available), liver transplant, and death will be compared to historical controls.
• PK of OCA and its conjugates.
• Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.</td><td></td></tr>
<tr><td>Section 12.1.3
Relationship of Adverse Events to Liver Biopsy</td><td>Insertion (new section)</td><td>The Investigator will document her/his opinion of relationship of an AE to liver biopsy using the criteria outlined in Table 9.
Table 9: Relationship of Adverse Events to Liver Biopsy<table><tr><th>Relationship</th><th>Description</th></tr><tr><td>Related</td><td>A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.</td></tr><tr><td>Not Related</td><td>Any event that does not meet the above criteria.</td></tr></table></td><td>Added with the addition of liver biopsies for the confirmation of progression to cirrhosis.</td></tr>
<tr><td>Section 12.1.5.2
Reporting of Serious Adverse Events</td><td>~~•Telephone: +1 858 964 1571~~
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.</td><td>If an SAE is reported by email or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible.</td><td>Updated to align with modified standard safety procedures.</td></tr>
<tr><td>Section 12.1.6
Suspected Liver-Related Clinical Outcome Events</td><td>Section 12.1.5
Given that the liver-related 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 liver-related clinical outcome events in order to retain the study</td><td>Section 12.1.6
Given that the liver-related clinical outcome events may also meet the criteria of a SUSAR, but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly, the Sponsor will not expeditiously report suspected</td><td>Updated to align with modified standard safety procedures and Sponsor standard language.</td></tr>
</table>

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	blind and preserve the integrity of the clinical outcomes endpoint. The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).	liver related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 **or oesophageal varices haemorrhage**), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological **or clinical** progression to cirrhosis (preferred term: hepatic cirrhosis).	
Section 12.1.8 Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	***Insertion (new section)***	**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 12.1.5.2.** **SAEs that occur in subjects 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 12.1.5.2.**	Updated to align with modified safety procedures and Sponsor standard language.
Section 12.1.9 Notification of Poststudy SAEs	***Section 12.1.7*** All SAEs that occur within 30 days following the ~~cessation of investigational product~~, whether or	***Section 12.1.9*** All SAEs that occur within 30 days following **discontinuation from the study,** whether or not	Updated to align with modified safety procedures

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.~~4.~~2. ~~SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.~~	they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.**5**.2.	and Sponsor standard language.
Section 12.2.7 Laboratory Assessments	The list of laboratory analytes to be tested is shown in Table 1~~0~~.	The list of laboratory analytes to be tested is shown in Table 1**1**, **and the normal reference ranges for liver biochemistries are shown in Appendix C.**	Added per Regulatory Authority request.
Section 13 Statistical Methods	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to ~~study database lock~~, propensity score determination, and unblinding of the double-blind subject treatment assignments.	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the **first interim analysis**, propensity score determination, and unblinding of the double-blind subject treatment assignments.	Reflects addition of interim analyses to the study protocol.
Section 13.1.1 Analysis Populations	***Insertion***	• **The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.**	The Per Protocol Population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.

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Section 13.1.1.1 Comparability of Historical Controls	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria ~~where possible~~.	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. **Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8**.	Clarifies the use of propensity scores in the assessment of the historical control population.
Section 13.1.5 Additional Secondary Efficacy Analyses	The following secondary efficacy analyses will compare ~~randomized~~ OCA ~~to randomized~~ placebo on using the ITT population:	The following **time-to-event** secondary efficacy analyses will compare OCA versus placebo using the ITT population: • **Progression to cirrhosis** • **Time to occurrence of HCC**	Editorial Change Progression to cirrhosis added as secondary endpoint in Version 3.1. HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	The association between ~~the effect of OCA on~~ ALP and bilirubin and the clinical benefit of OCA will be evaluated ~~by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This~~ analysis will be ~~based on~~ the ~~ITT population~~. Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.	The association between **biochemistry including** ALP and bilirubin **with clinical outcomes will be assessed** and the clinical benefit of OCA **using biochemistry as a surrogate endpoint** will be evaluated. **Detailed** analysis will be **described in** the **SAP**. Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of **OCA using biochemistry as a surrogate endpoint** for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.8 Supportive Analysis	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment. ~~Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a~~ full range of covariates across which the treatment and historical controls might differ. Only covariates and not outcome variables will be included in the propensity score estimation. ~~Therefore, there is no chance of biasing,~~ to avoid biased results that are in favor of one treatment.	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, **which serves as an external control for supportive analysis**. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment **between the treated subjects and the matched natural history subjects**. **A** full range of covariates across which the treatment and historical controls might differ **will be considered to mitigate potential bias**. Only covariates and not outcome variables will be included in the propensity score estimation **to avoid biased** results **that are** in favor of one treatment. **The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.** **A third-party statistician(s) will perform the propensity score modeling and matching. This**	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis. Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses. The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	
	The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes: • ~~Time to hepatocellular carcinoma~~		
Section 13.1.9 Handling of Dropouts or Missing Data	***Insertion***	**In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.**	Clarification of statistical analyses to address missing data.
Section 13.1.11 Examination of Subgroups	The primary and secondary efficacy endpoints will be analyzed for subject subgroups ~~(eg, age, sex, and race)~~ based on the ITT population. ***Insertion***	The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. **The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)** • **Early (normal albumin and normal bilirubin)**	Added per Regulatory Authority request.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Moderate (abnormal albumin or abnormal bilirubin)** • **Advanced (abnormal albumin and abnormal bilirubin)** **The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.** • **Monotherapy in patients who are intolerant or non-responsive to UDCA** • **Elderly patients** **Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.** **Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
Section 13.1.12 Continuous Monitoring and Interim Analyses	Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively. The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy ~~or futility~~) of the study beyond each interim analysis.	Both interim analyses will be pre-specified and will occur after accrual of 50% **(64 events)** and 75% **(96 events)** of clinical outcome events, respectively. The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation,	Added number of anticipated events. Clarification

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		modification, or cessation (for efficacy) of the study beyond each interim analysis	
Section 19 List of References	~~Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.~~ ***Insertion***	**Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Digestive and Liver Disease. 2015a;47(11):924-6.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6α-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-3572.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	Additional relevant references were added.
Appendix C Reference Laboratory Values from Central Laboratories	***Insertion (new appendix)*** ***Deletion:*** ***Appendix C in Version 3.1 has been deleted. It is now published as Protocol Addendum 2.***	***Appendix containing reference laboratory values from central laboratories added.***	Added per Regulatory Authority request.

APPENDIX I. SUMMARY OF CHANGES: PROTOCOL VERSION 3 TO PROTOCOL VERSION 4 (DATED 10 MAY 2017)

Please note that Protocol 747-302 Version 3.1 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. Therefore, a full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided below.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the modification of inclusion/exclusion criteria to expand the PBC disease spectrum, the addition of progression to cirrhosis as a secondary endpoint, and the addition of 2 interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

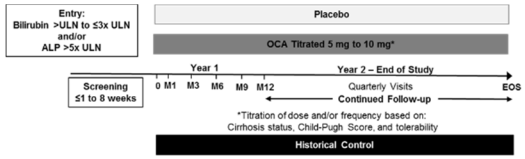
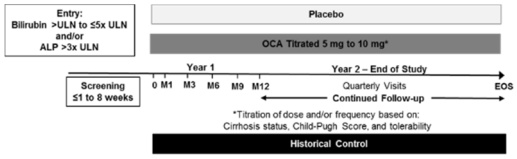
The text deleted from Protocol Version 3 is crossed out while revised text in Version 4 is indicated in bold font. Minor/editorial changes and non-substantial changes are not listed individually. For efficiency, rationales that impact multiple sections are provided below and referenced in the table with the corresponding rationale number.

1. **The phase of the study has been changed from "3b" to "4"** to reflect that this is a post-marketing study. Protocol 747-302 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC, ie, in the US and the EU. In all other regions, this study is considered Phase 3b. In May 2016, the FDA granted accelerated approval for OCA (Ocaliva) for the treatment of PBC. In December 2016, Ocaliva received Conditional Approval from the European Medicines Agency's Committee for Medicinal Products for Human Use.
2. **The term "primary biliary cirrhosis"** has been changed to "primary biliary cholangitis" to reflect recent changes in the nomenclature for PBC.
3. **The number of required adjudicated events for the final analysis has increased** from 121 to 127 due to the addition of two interim analyses, which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy) of the study. One interim analysis will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). In addition, inclusion of PBC subjects with earlier stage disease will increase the time to event, thereby requiring more events to maintain follow-up to approximately 6 years.
4. The first-year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by 2 years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.

5. "**Encephalopathy"** has been modified to "Hepatic Encephalopathy" to clarify that the relevant Clinical Outcome Event should be related to hepatic disease.
6. **Hepatocellular carcinoma** (HCC) has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.
7. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of HCC.
8. **Broadening the Spectrum of Disease**: Lowering the minimum allowable baseline ALP from >5x ULN to >3x ULN and raising the maximum allowable baseline total bilirubin to ≤5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the Phase 3 protocol 747-301. However, to ensure enrollment of an adequate number of subjects with abnormal total bilirubin, a minimum of 30% of the subjects enrolled in the study will have elevated bilirubin (>ULN) at Screening.
9. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
10. The increase in enrollment from 350 to 428 subjects is due in part to the increased number of events from two additional interim analyses, and in part due to the change in the estimated placebo baseline hazard rate, which resulted from changing the lower limit of ALP from >5x ULN to >3x ULN in the enrollment criteria #2.
11. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential noninvasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of Study 747-302.
12. **A Per Protocol (PP) population** has been added to the statistical analysis section. Sensitivity analysis for primary efficacy endpoints and key secondary efficacy endpoints will be performed using PP population.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD ~~PPD Clinical Operations,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~(Pacific time zone)~~ ~~Mobile:~~ ~~Fax:~~ PPD	**O**	The contact information of clinical operations and project managements personnel is no longer required per Sponsor's procedures.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Email:~~ PPD PPD		
Synopsis, Studied Period (Years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	Phase ~~3b~~	Phase **4**	Rationale 1
Synopsis, Objectives, Primary, Statistical Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• Encephalopathy (as defined by a West Haven score of ≥2) • ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5 Rationale 6
Synopsis, Objectives, Secondary	To assess the effect of OCA compared to placebo on time to first occurrence of each individual	To assess the effect of OCA compared to placebo on time to first occurrence of each individual	Rephrasing the objective

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 6.2 Secondary Objectives	component of the primary endpoint as listed above ~~and also~~ to include liver related death. ***Insertion*** To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects	component of the primary endpoint as listed above. **To assess the effect of OCA compared to placebo on time to occurrence of** liver-related death. **To assess the effect of OCA compared to placebo on progression to cirrhosis.** **To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).** To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 11 Rationale 6
Synopsis, Methodology: Schematic Diagram Section 7.1.1 Study Design Diagram, Figure 1	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching	**A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.**  Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN)**. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study	Rationale 8 Rationale 8 Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. • Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	visit following the Month 3 visit based on tolerability **and biochemical response** of the product. • Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (Planned) Section 7.2 Number of Subjects	***Insertion*** ***Change in Synopsis section*** Approximately ~~350~~ subjects	**In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the sub study may be added to the target subject enrollment number currently planned**. Approximately **428** subjects **are planned to be enrolled in the study.**	Rationale 10 and Addendum 2

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Change in Section 7.2 section It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study to achieve **127** adjudicated primary endpoint events.	
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ≤~~3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 8
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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: • ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~ • Intrauterine device (IUD)~~; 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 subject	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below: • **Barrier** method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide • Intrauterine device (IUD) • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) • Abstinence, if in line with the preferred and usual lifestyle of the subject	Standardizing language across protocols; removing double-barrier terminology.

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td>Synopsis, Exclusion Criteria

Section 8.3 Subject Exclusion Criteria</td><td>2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

3. Mean total bilirubin >~~3~~x ULN</td><td>2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

•History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria

3. Mean total bilirubin >**5**x ULN</td><td>This criterion (sub-bullet) is already included in Version 3 of the protocol. In the Version 4, it is added to the synopsis for consistency.

Rationale 8</td></tr>
<tr><td>Synopsis, Duration of Treatment</td><td>It is ~~estimated~~ that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue ~~121~~ total primary endpoint events.</td><td>It is expected that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 127 total primary endpoint events.</td><td>Rationale 3</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td>
<table>
<tr><th>Primary Objectives</th><th>Assessments</th></tr>
<tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)

• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~</td></tr>
<tr><td>Secondary Objectives</td><td></td></tr>
</table>
</td><td>
<table>
<tr><th>Primary Objectives</th><th>Assessments</th></tr>
<tr><td>Clinical outcomes</td><td>– Hepatic encephalopathy (as defined by a West Haven score of ≥2)</td></tr>
<tr><td>Secondary Objectives</td><td></td></tr>
<tr><td>Progression to cirrhosis</td><td>Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated</td></tr>
</table>
</td><td>Rationale 5

Rationale 11

Rationale 6</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		Hepatocellular carcinoma | **Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy**	
Synopsis, Statistical Methods Analysis Populations	The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), **Per Protocol (PP)** Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population. Rationale 12 (for PP Population)
Synopsis, Statistical Methods, Primary Efficacy Endpoint Section 11.1.1 Primary Assessments	The primary efficacy endpoint will be the time to first occurrence of one of the following ~~post randomization~~: • Encephalopathy (as defined by a West Haven score of ≥2) • ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~ ***Change in Synopsis section*** ~~Every event for enrolled subjects~~ will be adjudicated by an independent committee.	The primary efficacy endpoint will be the time to first occurrence of one of the following: • **Hepatic** encephalopathy (as defined by a West Haven score of ≥2) **All events** will be adjudicated by an independent committee.	Rationale 5
Synopsis, Statistical Methods, Primary Efficacy Analysis Section 13.1.3 Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population. ***Insertion***	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. **The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	Rationale 12

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses Section 13.1.4 Secondary Efficacy Analysis	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints. ***Insertion***	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints. **The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	Rationale 12
Synopsis, Statistical Methods, Additional Efficacy Analyses Section 13.1.5 Additional Secondary Efficacy Analyses	~~Other~~ Efficacy Analyses The following secondary efficacy analyses will compare OCA to placebo ~~on time to the following events~~: ***Insertion***	**Additional** Efficacy Analyses The following **time-to-event** secondary efficacy analyses will compare OCA to placebo **using the ITT population**: • **Progression to cirrhosis** • **Time to occurrence of HCC** **Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as Baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for**	Rationale 6 and Rationale 11 Rationale 11

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. **For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2.**	
Synopsis, Statistical Methods, Safety Analyses	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will ~~compare OCA and placebo using~~ the Safety Population.	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will **be summarized by treatment group for** the Safety Population.	Clarification of summary analyses.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to ~~clinical outcomes~~. In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	**The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN.** The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **of subject** accrual and 6 years of follow up. • **Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.** • **A dropout rate of 10% is assumed** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to **liver-related outcomes, including all-cause mortality**. In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	Rationale 8 Rationale 4 Rationale 3
Section 5.1 Overview of PBC and OCA	5.1. Overview of Primary Biliary ~~Cirrhosis~~ and Obeticholic Acid	5.1. Overview of Primary Biliary **Cholangitis** and Obeticholic Acid	Updating language to include accelerated and conditional

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis) 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. ursodeoxycholic acid (UDCA), a physiological constituent of human bile, ~~is currently the only treatment approved for PBC~~ (Lindor 2009). While UDCA therapy ~~has~~ a marked effect on the treatment of PBC, up to 50% of patients ~~show~~ a suboptimal response or no response to UDCA. Such patients ~~are~~ at significantly increased risk of a poor clinical outcome due to PBC disease progression. ~~There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]).~~ Obeticholic acid (OCA)~~ is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.~~ ~~OCA is a modified bile acid and~~ farnesoid X receptor (FXR) agonist ~~that is~~ derived from the primary human bile acid chenodeoxycholic acid (CDCA~~). OCA is currently being developed in the United States (~~US~~) and Europe for the treatment of PBC and other chronic liver diseases. OCA has~~	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. **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), **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 (Pellicciari 2002). 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**	approvals of OCA in the US and EU.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States~~ Food and Drug Administration (FDA) ~~has~~ granted accelerated approval for Ocaliva ~~for the treatment of PBC.~~ Ocaliva ~~is not yet approved outside the United States for use in any~~ indication.	**UDCA. In December 2016, the European Commission granted conditional approval for** Ocaliva **for the same** indication.	
Section 5.4 Overview of PBC and OCA	As of 31 Jan ~~2016~~, approximately ~~1726~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ subjects had PBC, ~~330~~ subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease ~~(NAFLD)~~, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~20~~ subjects had primary sclerosing cholangitis (~~PSC~~).	As of 31 Jan **2017**, approximately **2186** subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** subjects had PBC, **686** subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **52** subjects had primary sclerosing cholangitis, **and 5 subjects had biliary atresia.** **----------** **[1]Includes estimated numbers from ongoing blinded studies.**	Language updated to include data from current IB.
Section 5.5.2.1 Rationale for OCA Dose	The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; ***Insertion***	The Phase 3 PBC study **(Study 747-301)** subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; **Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus.**	Provides rationale for the dosing in alignment with commercial labeling.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Based on these data, ~~the indicated commercial doses of~~ OCA for the treatment of patients with PBC are 5 mg and 10 mg. ~~As such,~~ Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.	Based on these data, the **approved dosing regimen for** OCA for the treatment of patients with PBC are 5 mg and 10 mg. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose **for at least 3 months**, increasing to 10 mg OCA, if tolerated.	
Section 5.6 Summary of Known Potential Risks with OCA	These findings were seen more frequently with doses ~~above~~ 10 mg OCA. ***Insertion***	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).** **Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.**	Language has been updated to reflect Sponsor standards.
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3).	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5x** ULN and/or ALP >**3**x ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). . . **A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.** **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**…based	Rationale 1 and Rationale 8 Rationale 10 Rationale 8 Clarification Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		on tolerability **and biochemical response** (see Section 7.3)	
	The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 3
Section 7.1.2 Schedule of Study Procedures, Table 1	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration** • **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.
	[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility.	[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. **Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility.**	
	[j] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments at Day 0 and Month 12).
	[k] Endoscopy will be conducted at ~~selected~~ study sites where the device is available.	[m] Endoscopy will be conducted at **all** study sites where the device is available**.**	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met~~.	[m] 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**.	
	[o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. …	[p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. …	Rationale 9
	[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a Baseline (eg, Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.**	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions***	Physical exams have been added at **1-Month Post Titration** Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.
	[i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Not required if done within 6 months of visit.~~ ***Insertion*** (subsequent footnotes are renumbered accordingly)	[i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. [j] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available.**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis. DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments).
	~~[j]~~ Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices.	[k] Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices.	
	[k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met.~~	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. 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**. [o] … The initial dose titration of investigational products may occur at the Month 3 visit, or any	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[e] … The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability.	study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response.**	Rationale 9
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study to achieve **127** adjudicated primary endpoint events. **In the event additional subjects are needed to complete enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned**.	Rationale 10 Language added to allow for continued enrollment into the biopsy substudy; additional subjects are not anticipated to prolong the duration of the study.
Section 7.3 Planned Dosing Regimen, and Table 3	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. ***Footnotes of Table 3 were re-ordered*** [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin are >ULN**. [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 7.4 Dose Titration Criteria	***Insertion*** 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.	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.** 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, **biochemical response**, and clinical judgment. **Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).**	Added language to clarify titrations (up or down).
Section 7.4.1 Pre-Titration Tolerability	• There must be no clinically significant increase (as determined by the ~~i~~nvestigator) in the subject's liver function tests. ~~Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be~~	• There must be no clinically significant increase (as determined by the **I**nvestigator) in the subject's liver function tests.	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Assessment Requirements	~~up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19 should be implemented, as required.~~		
Section 7.4.2 Safety Criteria for Adjustment or Stopping Doses	***The text in this section is moved to Section 8.4.***		To avoid redundancy
Section 7.5 Criteria for Study Termination	The window of time for scheduling the visit will be based on a final projection of when the requisite ~~121~~ adjudicated events will have been accrued.	The window of time for scheduling the visit will be based on a final projection of when the requisite **127** adjudicated events will have been accrued.	Rationale 3
Section 8.4 Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	**[*Moved from Section 7.4.2 of Version 3*]** Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be **adjusted back** to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved. Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an **outcome** event, he or she should continue the regular visit schedule and continue taking investigational product as long as the **subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the** Investigator assesses it as safe. In general, subjects should be	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		strongly encouraged to both stay on investigational product and remain in the study until study termination.	
Section 8.4.1.1 Reasons for Additional Monitoring Related to Liver Chemistries	***Modification of 8.4.2.1 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.~~	**Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored.**	Clarified guidelines for subjects who develop elevations in liver chemistries. Language related to interruption of investigational product is now located in Section 8.4.1.2.
Section 8.4.1.2 Reasons for Investigational Product Interruption Related to	***Insertion***	**Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3x baseline (and >ULN)**	Clarified guidelines for subjects who develop elevations in liver chemistries.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Elevated Liver Chemistries		• **Total bilirubin >2x 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 AE information should also be collected and the subject 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 >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 study medication and no other cause for the elevation is identified, it may be assumed that the elevations were due**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		to disease progression and the subject 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.** **If at any time a subject 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.** **Subjects who develop evidence of severe drug-induced liver injury, which 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**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		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 subjects 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 subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.** **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**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		adjudicated by the Hepatic Safety Committee (see Section 13.4).	
Section 8.4.1.3 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~	**8.4.1.3 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product **immediately,** but should continue with the study visit schedule. **As described in Section 12.1.11** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.11.**	Clarification regarding prolonged interruption in investigational product such as in the event of pregnancy.
Section 8.4.2.1 Liver Transplantation	***Text Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product*** Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.	**8.4.2.1 Liver Transplantation** Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.	The relocation of this statement from within Section 8.4.2 to 8.4.2.1 clarifies procedure to discontinue subjects who undergo a liver transplant, from investigational product but not study visits.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 8.4.3 Other Reasons for Discontinuation of Study or Investigational Product	8.4.2 Other Reasons for Discontinuation of Study or Investigational Product ~~Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).~~ The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or~~ cardiovascular events.	**8.4.3** Other Reasons for Discontinuation of **Study or** Investigational Product The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess **suspected major adverse**	Clarification of process

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.~~	cardiovascular events **(MACE) and liver-related clinical outcomes.** – **Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.18).** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	
Section 9.7.1 Visit Windows	Screening	Screening **See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.**	
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of ~~the study~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis.
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as noncirrhotic at Baseline per the criteria listed in Section 9.7.3.1 exhibits any signs or symptoms associated with progression to cirrhosis, as defined by the same criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy (centrally read) unless not medically indicated. Laboratory samples needed to obtain noninvasive scores of liver**	Details the assessment of progression to cirrhosis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis. **Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.** **Sites participating in the paired biopsy substudy must confirm progression to cirrhosis by biopsy as per the information outlined in protocol Addendum 2.** **All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	
Section 9.7.6 Screening Procedures	~~Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated~~ serum chemistry samples (at least 2 weeks apart) ~~to confirm~~ pretreatment ALP and total bilirubin values: ***Insertion*** • The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and	**Collection of 2 s**erum chemistry samples (**collected** at least 2 weeks apart**) during Screening is required for confirmation of the** pretreatment **serum chemistry values, including the** ALP and total bilirubin **used to determine eligibility**: • **When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Allows repeat assessments when baseline laboratory values are discrepant between Screening Visit 1 and Screening Visit 2.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN). • …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (~~selected~~ study sites ~~only~~), ***Insertion***	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5x** ULN and/or an ALP >**3x** ULN). • …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 **(at all** study sites **where the device is available**), **In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.**	
Section 9.7.7 Day 0 Procedures	• Perform ~~transient elastography (~~TE~~;~~ at ~~selected~~ study sites~~, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at ~~selected~~ study sites~~,~~ where device is available); • Perform an esophagogastroduodenoscopy (endoscopy; at ~~selected~~ study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.	• Perform TE at **all** study sites **with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at **all** study sites where **the device is** available); • Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where **device is** available) to assess the presence or absence of oesophageal varix/varices.	Clarifies use of TE and modifies the time during which an historic TE report remains valid. Clarifies the use of DEXA and endoscopy.
Section 9.7.8 Month 1 Procedures Section 9.7.10	9.7.10 Post-Titration visit Procedures ***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced	9.7.10 **1-Month** Post-Titration visit Procedures • Perform a physical examination. • In the event it is not feasible for the subject to return to the site for the above referenced	Physical Exams have been added one month after each dose adjustment for added safety monitoring. Options for safety monitoring assessments are provided

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
1-Month Post-Titration visit Procedures	procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements: ***Insertion (9.7.8)*** ***Insertion (9.7.10)***	procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit **laboratory** requirements: - **A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed**. - **A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed**.	when returning to the site presents significant burden on the subject.
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion*** ***Insertion in 9.7.11 (not 9.7.16)***	• **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).** • **Perform a physical examination**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis. Hepatic ultrasound has been increased to every 6 months to conform to AASLD and EASL guidelines for PBC patients with cirrhosis.
Section 9.7.12 Month 9 Procedures Section 9.7.14 Month 12 Procedures Section 9.7.16 Month 16 Continued	*...DEXA procedure to be done at* ~~selected~~ study sites ~~only~~,	*...DEXA procedure to be done at* **all** study sites **where the device is available**	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Follow-Up Procedures			
Section 9.7.14 Month 12 Procedures Section 9.7.17 Month 12 Follow-up Procedures Section 9.7.18 EOS/EOT	• Perform TE ~~(~~at ~~selected~~ study sites~~, where available) using the~~ Fibroscan® TE device. ***Additional edit in Section 9.7.18*** - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF ~~and remind the subject that fasting is required prior to all study visits~~.	• Perform TE at **all** study sites **with access to the** Fibroscan® TE device. - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.	Clarification
Section 10.3 Investigational Product Storage	~~The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical study 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.**	Updating temperature excursions language per Sponsor stability studies.
Section 11.1.2 Secondary Assessments	***Insertion***	• **Individual components of the primary endpoint.** • **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.**	Rationale 11

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in Addendum 2).** – **HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.**	Reflects addition of a biopsy substudy available to interested sites in Addendum 2.
	• Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ~~and~~ ELF, Fibroscan (and others as determined during the course of the study).	• Biomarkers, including **other** markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ELF, **and** Fibroscan (and others as determined during the course of the study). • **Clinical outcomes, including individual component of the primary endpoint (where available), liver transplant, and death will be compared to historical controls.** • **PK of OCA and its conjugates.**	
	• Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.	• Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.	
Section 12.1.3 Relationship of AEs to Liver Biopsy	***Insertion (new section)***	**The Investigator will document her/his opinion of relationship of an AE to liver biopsy using the criteria outlined in Table 9.** **Table 9: Relationship of Adverse Events to Liver Biopsy**	Added with the addition of liver biopsies for the confirmation of progression to cirrhosis.

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td></td><td><table><tr><th>Relationship</th><th>Description</th></tr><tr><td>Related</td><td>A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.</td></tr><tr><td>Not Related</td><td>Any event that does not meet the above criteria.</td></tr></table></td><td></td></tr>
<tr><td><u>Section 12.1.5.2</u>
Reporting of Serious Adverse Events</td><td>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
~~•Telephone: +1 858 964 1571~~
~~Investigational new drug (IND) Safety Reports~~

Insertion</td><td>If an SAE is reported by email or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible

Redacted medical record source documentation will be requested for all SAEs and emergency room visits.</td><td>Updated to align with modified standard safety procedures.

Added sentence regarding redacted medical records to align with Sponsor safety standards.</td></tr>
<tr><td><u>Section 12.1.6</u>
Suspected Liver-Related Clinical Outcome Events</td><td>~~For~~ liver-related clinical outcome events ~~could~~ also meet the criteria of a SUSAR, ~~which would necessitate unblinding for expedited reporting, please refer to Section 11.1.2.4.~~</td><td>Given that the liver-related clinical outcome events may also meet the criteria of a SUSAR, but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly, the Sponsor will not expeditiously report suspected liver-related 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 “study event” on the AE CRF and will be submitted for</td><td>Updated to align with modified standard safety procedures and Sponsor standard language.</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		adjudication to the Hepatic Outcomes Committee as described in Section 13.4. The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 **or oesophageal varices haemorrhage**), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological or clinical progression to cirrhosis (preferred term: hepatic cirrhosis).**	
	The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), ~~and~~ spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).		
Section 12.1.8 Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	***Insertion (new section)***	**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 12.1.5.2.** **SAEs that occur in subjects 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 12.1.5.2.**	Updated to align with modified safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 12.1.9 Notification of Poststudy SAEs	All SAEs that occur within 30 days following the ~~cessation of investigational product~~, 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 12.1.~~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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours). ~~SAEs that occur more than 30 days after a subject has discontinued study medication, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with study medication, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.~~	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 12.1.**5**.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 12.1.5.2.	Updated to align with modified safety procedures and Sponsor standard language.
Section 12.1.10 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver**	Updated to align with modified standard safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		injury, indicating that liver injury was related to underlying liver disease.	
Section 12.1.11 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 8.4.1.3and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing or emailing~~ to ~~the Sponsor at +1 800 497 8521 or~~ sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use~~ of investigational product. ~~The subject may reinstate investigational product after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose~~ pregnancy is terminated early (planned or unplanned) ~~may be permitted to resume participation in the study if~~ termination of the pregnancy ~~is~~ confirmed by a serum β-hCG test ~~(see Section 8.4.1).~~	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** sae@interceptpharma.com **or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor**. **The subject 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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**	Updated to align with modified standard safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		reporting procedures described in Section 12.1.5 must also be followed.	
Section 12.2.7 Laboratory Assessments	The list of laboratory analytes to be tested is shown in Table 1~~0~~.	The list of laboratory analytes to be tested is shown in Table 11, **and the normal reference ranges for liver biochemistries are shown in Appendix C.**	Added per Regulatory Authority request.
Section 12.2.7 Table 10 List of Laboratory Analytes	~~Measurement of Liver Fibrosis~~ / ~~Fibroscan~~ ~~Bone Density Assessment~~ / ~~DEXA~~ Other / ***Insertion***	***Deletion*** Other / **OCA-glucuronide**	Measurements of liver fibrosis are captured in a different section. OCA-glucuronide was listed in the text but missing from the table.
Section 13 Statistical Methods	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior ~~to study database lock~~, propensity score determination, and unblinding of the double-blind subject treatment assignments.	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to **the first interim analysis**, propensity score determination, and unblinding of the double-blind subject treatment assignments.	Reflects addition of interim analyses to the study protocol.
Section 13.1.1 Analysis Populations	• ~~The Randomized Population will include all randomized subjects~~ ***Insertion***	***Deletion*** • **The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.**	Rationale 12

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.1.1 Comparability of Historical Controls	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria ~~where possible~~.	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. **Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8**.	Clarifies the use of propensity scores in the assessment of the historical control population.
Section 13.1.2.1 Sample Size Monitoring	13.1.2.1 Sample Size ~~Re-Estimation Plan~~ Therefore, ~~starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups. ~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.~~	13.1.2.1 Sample Size **Monitoring** Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of **127** adjudicated events for the final analysis in the combined groups. ***Deletion***	Clarifies the ongoing monitoring of event rate and sample size.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~		
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion (new subsection)***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between biochemistry including ALP and bilirubin with clinical outcomes will be assessed and the clinical benefit of OCA using biochemistry as a surrogate endpoint will be evaluated. Detailed analysis will be described in the SAP.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA using biochemistry as a surrogate endpoint for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
Section 13.1.8 Supportive Analysis	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment. ~~Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process~~	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, **which serves as an external control for supportive analysis**. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment **between the treated subjects and the matched natural history subjects**. **A** full range of covariates across which the treatment and historical controls might differ **will be considered to mitigate potential bias**.	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis. Clarifies the use of the historical controls as an external control in supportive

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~is to successfully mitigate potential bias, it has to be done considering~~ ~~a~~ full range of covariates across which the treatment and historical controls might differ. Only covariates and not outcome variables will be included in the propensity score estimation. ~~Therefore, there is no chance of biasing,~~ to avoid biased results that are in favor of one treatment. The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	Only covariates and not outcome variables will be included in the propensity score estimation **to avoid biased** results **that are** in favor of one treatment. **The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.** **A third-party statistician(s) will perform the propensity score modeling and matching. This third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses.** The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	• ~~Time to hepatocellular carcinoma~~ ***(Text from Section 13.1.9 [Alternative Primary Analysis] modified and included in this section)*** ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new~~ primary efficacy ~~analysis will become the comparison of~~ all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause~~) (see Section 13.1.2.1~~). similar statistical methodology as specified above ~~in Section 13.1.8 for supportive analyses will be utilized~~. ~~The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct** based on **the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised** primary efficacy analysis. **This analysis would compare** all subjects in **the** OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), **using** similar statistical methodology as specified above. **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
Section 13.1.9 Handling of Dropouts or Missing Data	***Insertion***	**In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.**	Clarification of statistical analyses to address missing data.
Section 13.1.11 Examination of Subgroups	The primary and secondary efficacy endpoints will be analyzed for subject subgroups **(eg, age, sex, and race)** based on the ITT population. ***Insertion***	The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. **The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)** • **Early (normal albumin and normal bilirubin)** • **Moderate (abnormal albumin or abnormal bilirubin)** • **Advanced (abnormal albumin and abnormal bilirubin)** **The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.**	Added per Regulatory Authority request.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Monotherapy in patients who are intolerant or non-responsive to UDCA** • **Elderly patients** **Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.** **Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.**	
Section 13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs, and/or loss of subjects to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% (64 events) and 75% (96 events) of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for**	Two Interim Analyses have been added to the protocol.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		efficacy) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.	
Section 19 List of References	***Insertion***	**Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Digestive and Liver Disease. 2015a;47(11):924-6.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.** **Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6α-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-3572.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	Additional relevant references were added.
Appendix A	Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg	Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg	Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment	OCA or matching placebo once daily, based on tolerability.	OCA or matching placebo once daily, based on tolerability **and biochemical response**.	
Appendix B List of Study 747-302 Outcome Events	***This Appendix with the following information has been deleted.*** ~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~		Redundant; Information is contained within the protocol.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Hepatocellular carcinoma~~		
Appendix C Reference Laboratory Values from Central Laboratories	***Insertion (new appendix)***	***Appendix containing reference laboratory values from central laboratories added.***	Added per Regulatory Authority request.

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Version 5: 04 January 2018

EudraCT Number: 2014-005012-42

Sponsor

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

TEL: +1 858 250 6398

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

01 Feb 2018

PPD PhD

Date

PPD 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 747-302. 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor – 24-hour Emergency Reporting

Primary Contact**:**	PPD MD, MPH| Senior Medical Director / Medical Affairs Syneos Health | Chapel Hill, NC 27514 |U.S.A. Tel: PPD Mobile: PPD PPD
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SAE Fax:	+1 800 497 8521
SAE Email:	sae@interceptpharma.com

2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid (OCA)

Name of Active Ingredient:

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

Title of Study:

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

Investigators and/or Study Center(s):

Approximately 170 investigational study sites, globally.

Studied Period (Years):	**Phase of Development:**
The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Phase 4: US, Canada, and the EU Phase 3b: All other regions

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cholangitis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

Secondary

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above.

To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.

To assess the effect of OCA compared to placebo on progression to cirrhosis.

To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To characterize the pharmacokinetics (PK) of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

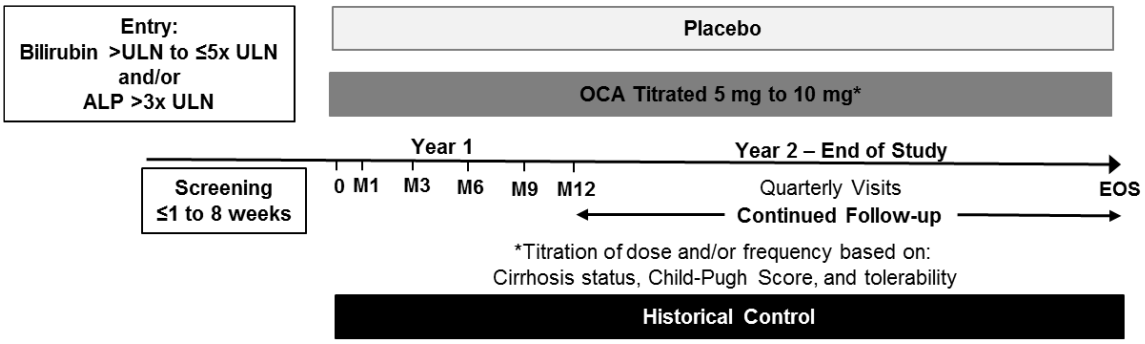
To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened twice during a 1- to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3).

Investigational product will be taken orally, once daily for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (> upper limit of normal [ULN]/ ≤ULN). A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.

Schematic Diagram Study 747-302:



EOS = end of study; ULN = upper limit of normal
Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN). Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:

- Noncirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.
- For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.
- Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B or Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly (at least 3 days apart), based on tolerability and biochemical response.

Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Planned Dosing Regimen	
	Standard	**Modified**
	Noncirrhotic/ Child-Pugh A	**Child-Pugh B or Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly

[a] Starting dose based on subject's cirrhosis status and Child-Pugh Score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or 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 Subjects (Planned):

Approximately 428 subjects are planned to be enrolled in the study. In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
   - Intrauterine device (IUD)
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence, if in line with the preferred and usual lifestyle of the subject
6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:

- Hepatitis C virus infection
- Active hepatitis B infection; however, subjects 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
- Nonalcoholic steatohepatitis
- Gilbert's Syndrome

2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy
     – Spontaneous bacterial peritonitis
   - Known or suspected HCC
   - Prior transjugular intrahepatic portosystemic shunt procedure
   - Hepatorenal syndrome (type I or II) or Screening (Visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)
3. Mean total bilirubin >5x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphocytic leukemia)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months prior to Day 0)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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-month 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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
14. UDCA naïve (unless contraindicated)

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Reference Therapy, Dosage and Mode of Administration:

Placebo (matching tablets)

Duration of Treatment:

It is expected that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 127 total primary endpoint events.

Criteria for Evaluation:

Primary Objectives	**Assessments**
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Progression to cirrhosis	Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (ie, Fibroscan® transient elastography [TE]) confirmed by biopsy unless not medically indicated
HCC	Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy
Change in baseline liver biochemistry	Liver biochemistry (see Table 12 for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhanced liver fibrosis (ELF), and Fibroscan® TE
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
PK	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events including adverse events of special interest Clinical laboratory values

Statistical Methods:

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP), Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBC Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Efficacy Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

All events will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 its 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Additional Secondary Efficacy Analyses

The following time-to-event secondary efficacy analyses will compare OCA versus placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)

- Time to development of varix/varices
- Progression to cirrhosis
- Time to occurrence of HCC
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as Baseline TE where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at Baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.

For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2.

Further details on efficacy, health outcomes, and PK analyses are specified in Section 13.

Safety Analyses

Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vitals, electrocardiogram, and clinical laboratory results will be summarized by treatment group for the Safety Population.

Sample Size Justification

The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN. The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years of subject accrual and 6 years of follow-up
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.
- A dropout rate of 10% is assumed.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
CAC	Cardiovascular Adjudication Committee
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DILI	Drug-induced liver injury
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
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FIS	Fatigue Impact Scale
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	Investigator's 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
LDL	low-density lipoprotein
LTSE	long-term safety extension
MACE	major adverse cardiovascular events
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SUSAR	suspected unexpected serious adverse reaction
tauro-OCA	taurine 6α-ethyl chenodeoxycholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event

Abbreviation or Specialist Term	Explanation
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 Primary Biliary Cholangitis and Obeticholic Acid

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 United States (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.

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), 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 (Pellicciari 2002). 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 747-302 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. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 13 Oct 2017, approximately 2690 subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, 552 subjects had PBC, 1141 subjects had NASH, 41 subjects had diabetes mellitus/nonalcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and 73 subjects had primary sclerosing cholangitis, and 6 subjects 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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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.

[1] Includes estimated numbers from ongoing blinded studies.

Study 747-301 (216 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects reaching specific criteria for ALP and bilirubin (ALP <1.67× 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 <1.67× 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 10 mg OCA 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. The LTSE phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rationale for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. As a result, starting subjects on 5 mg OCA and titrating to 10 mg based on tolerability and clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate

biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Dose

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study (Study 747-301) subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus. Based on these data, the approved dosing regimens for OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose for at least 3 months, increasing to 10 mg OCA, if tolerated.

5.5.2.2. Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh Score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic

impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).

5.5.2.3. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Importance of Monitoring of Disease Progression

Given PBC is a chronic, progressive liver disease, it is important that subjects with PBC are closely monitored to ensure early identification of potential disease progression to cirrhosis, decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve subject oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules based laboratory monitoring.

Subjects will be monitored for potential hepatic injury and/or decompensation and progression to cirrhosis (Section 7.5). Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 7.6 and Section 7.7. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.

5.7. Summary of Known Potential Risks with OCA

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

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

6.2. Secondary Objectives

To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above.

To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.

To assess the effect of OCA compared to placebo on progression to cirrhosis.

To assess the effect of OCA compared to placebo on time to occurrence of HCC.

To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.

To characterize the PK of OCA and its conjugates in a subset of subjects.

To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.

To assess the safety and tolerability in subjects treated with OCA compared to placebo.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 4, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤5x ULN and/or ALP >3x ULN. Subjects enrolled will be at higher risk of liver-related clinical complications.

Approximately 428 subjects meeting all enrollment criteria will be recruited into the study over an approximate 4-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). Subjects will be screened during a 1- to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). Randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening. In addition to the placebo control arm, multiple historical control groups (concurrent and retrospective) will be used.

Subjects will be dosed according to their cirrhosis status and Child-Pugh Score. Subjects who are noncirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo. Following 3 months of once daily treatment with investigational product, the dose should be titrated to a maximum 10 mg OCA or matching placebo once daily, based on tolerability and biochemical response (see Section 7.3).

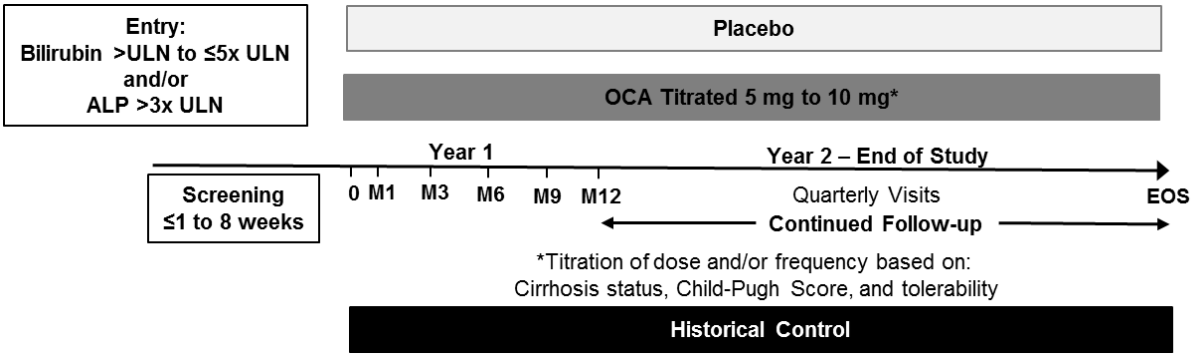
Subjects with cirrhosis (see Section 7.5.4) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.

It is anticipated that subjects will be followed for a minimum of approximately 6 years. The study will continue until approximately 127 adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.

This study will be conducted at approximately 170 international study sites with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, and networks.

7.1.1. Study Design Diagram

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; ULN = upper limit of normal

Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (Up-titration should be considered when ALP and/or total bilirubin are >ULN). Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2)

	Screening Visits		Day 0	M 1	M2	M 3	Post-Titration Visits[b]	M 6	M 9	M 12
	1	2[a]								
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Informed Consent	X									
Medical/PBC History[d]	X									
Cirrhosis Status Assessment[e]	X									
Inclusion/Exclusion Criteria	X	X	X							
Physical Exam	X			X	X		X	X		X[d]
Assessments for Child-Pugh Score[f]	X		X	X	X	X	X	X	X	X
Vital Signs (including weight)	X[g]		X			X		X	X	X[g]
12-Lead Electrocardiogram	X									X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X					X		X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[h]			X							X
Fibroscan® TE[i]			X					X		X
Endoscopy[j]			X							X
Hepatic Ultrasound[k]		X						X		X
Gallbladder Assessment (Ultrasound)		X[k]								
Adverse Events	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Health Outcome Assessments[l]			X			X		X	X	X

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2) (Continued)

	Screening Visits		Day 0	M 1	M2	M 3	Post-Titration Visits[b]	M 6	M 9	M 12
	1	2[a]								
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**±1 wk**	**±1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Randomization/Treatment Assigned			X							
Dose Titration: Standard Dosing[m,n]						X		X (if applicable)		
Dose Titration: Modified Dosing (if applicable)[n,o]						X		X	X	X
Dispense Investigational Product[o]			X			X		X	X	X
IP Accountability/Compliance				X	X	X	X	X	X	X
Dosing Diary			X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS[p]										
Urinalysis	X		X							X
Urine-based β-hCG Pregnancy Test[q]	X		X							
Chemistry/Hematology/Coagulation[p]	X	X[a]	X	X	X	X	X	X	X	X
Amylase and Lipase			Sample to be collected if the subject experiences acute pancreatitis or cholecystitis							
Review Progression to Cirrhosis Algorithm				X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X			X		X	X[r]	X
Markers of Hepatic Fibrosis and/or Inflammation[s]			X					X		X
Genetics[t]			X							X

AE = adverse event; ALP = alkaline phosphatase; β-hCG = beta human chorionic gonadotropin; eCRF = electronic case report form; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; HCC = hepatocellular carcinoma;
IP = Investigational Product; M = month, MRS = Mayo Risk Score; TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Refer to Section 9.7.3 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] Post-Titration visits must be performed 1 month (± 1 week) and 2 months (±1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. See Appendix A for additional guidance. In subjects following the standard dosing regimen, the Post-Titration Visit must be performed 1 month (±1 week) and 2 months (±1 week) after the first up-titration to 10 mg OCA or matching placebo.
[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.
[d] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.
[e] Presence or absence of cirrhosis should be assessed per Section 7.5.4. Cirrhosis status should be repeated as clinically indicated.
[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] Height will be collected at this visit.
[h] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.5).
[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for this procedure.
[j] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.4 for additional information related to the allowed window at Day 0 for this specific procedure.
[k] Ultrasound will be conducted to enhance HCC surveillance and for gallbladder assessment at Screening. If ultrasound was not performed at Screening and the historic ultrasound is >3 months from Day 0, perform a hepatobiliary ultrasound at the Day 0 visit.
[l] Health Outcome Assessments: Data related to nonstudy related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.
[m] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.
[n] Dose Titration is based on cirrhosis status (Section 7.5.4) and Child-Pugh Score (Section 7.5.5). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.
[o] Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.
[p] The subject 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. MELD and MRS values will be calculated based on serum chemistry and coagulation values at each visit.
[q] Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at the central laboratory. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
[r] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.10 for the PK sampling schedule.
[s] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.
[t] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. If a Baseline (eg, Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2)

	Year 2 Through End of Study					
	M 3 continued follow-up	**Post-Titration Visits[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Physical Exam[d]		X			X	X
Assessments for Child-Pugh Scores[e]	X	X	X	X	X	X
Vital Signs (including weight)			X		X[f]	X[f]
12-Lead Electrocardiogram					X	X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[g]					X	X
Fibroscan®TE[h]			X		X	X
Endoscopy[i]					X	
Hepatic Ultrasound[j]			X		X	X
Adverse Events	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Health Outcome Assessments[k]	X		X	X	X	X
Dose Titration (if applicable)[l]	X		X	X	X	
Dispense Investigational Product	X		X	X	X	
IP Accountability/Compliance	X	X	X	X	X	X
Dosing Diary	X	X	X	X	X	X
LABORATORY EVALUATIONS[m]						
Urinalysis					X	X
Chemistry/Hematology/Coagulation[m]	X	X	X	X	X	X
Amylase and Lipase	Sample to be collected if the subject experiences acute pancreatitis or cholecystitis					
Review Progression to Cirrhosis Algorithm	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)[m]					X	X

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2) (Continued)

	Year 2 Through End of Study					
	M 3 continued follow-up	**Post-Titration Visits[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Markers of Hepatic Fibrosis and/or Inflammation[n]			X		X	X
Genetics[o]					X	

AE = adverse event; β-hCG = beta human chorionic gonadotropin; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, MRS = Mayo Risk Score; TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] Post-Titration Visits must be performed 1 month (±1 week) and 2 months (±1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. See Appendix A for additional guidance. In subjects following the standard dosing regimen, the Post-Titration visit must only be performed 1 month (±1 week) and 2 months (±1 week) after the first up-titration to 10 mg OCA or matching placebo.

[b] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] The yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] 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 case report form.

[f] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.5).

[g] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available.

[h] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices.

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

[j] Health Outcome Assessments: Data related to nonstudy related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[k] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[l] Dose Titration is based on cirrhosis status (see Section 7.5.4) and Child-Pugh Score (Section 7.5.5). The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

[m] The subject should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, but water is permitted. MELD and MRS values will be calculated based on serum chemistry values at each visit.

[n] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[o] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.

7.1.3. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 428 subjects will be randomized in the study to achieve 127 adjudicated primary endpoint events. In the event additional subjects are needed to complete enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

7.3. Planned Dosing Regimen

Subjects will be randomized to treatment with either OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined Section 7.5.4) and applicable Child-Pugh Score (see Section 7.5.5) as outlined in Section 7.4.

Table 3: Planned Dosing Regimen by Cirrhosis and Child Pugh Score

	Scheduled Dosing Regimen	
	Standard	**Modified**
	Noncirrhotic/ Child-Pugh A	**Child-Pugh B or Child-Pugh C**
Starting Dose[a] (Day 0)	5 mg daily	5 mg once weekly
Titration 1[b] (≥Month 3)	10 mg daily	5 mg twice weekly[c]
Titration 2[b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly[c]

[a] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4).
[c] Dosing per the twice weekly schedule must be at least 3 days apart.

Non-Cirrhotic or Child-Pugh A

Subjects who are noncirrhotic or classified as Child-Pugh A at screening will receive 5 mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product and assessment of biochemical response. Up-titration should be considered when ALP and/or total bilirubin are >ULN. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the investigational product tolerability assessment before up-titration can occur (see Section 7.4.1).

For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.

Cirrhotic and Child-Pugh B or C

Subjects with cirrhosis (see Section 7.5.4) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, initiating 5 mg OCA or matching placebo once weekly. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

The dosing regimen should be determined as described shown in Table 13 Appendix A. Investigators should follow the dosing/titration schedule as shown described in Section 7.4 and Appendix A.

7.4. Dose Titration 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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 7.5.4 and Section 7.5.5) or Child-Pugh 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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3. A 1-Month and 2 Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.7).

Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability; see Section 7.4.1).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 7.5.4) or Child-Pugh Score (Section 7.5.5) dosing should be reassessed and the dosing regimen modified appropriately. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change to the dosing regimen. 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, biochemical response, and clinical judgment.

Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 7.5.4. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the Investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).

Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters (eg, increase in vitamin K resulting in change in INR) should be documented appropriately and discussed with the Medical Monitor before any continuation or change to the dosing regimen (Appendix A).

Child-Pugh Scores will be calculated during screening, at each scheduled study visits, and at unscheduled visits in the event of signs or symptoms of suspected hepatic injury or decompensation are present. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 7.5.4) and/or Child-Pugh Score is observed independent of a study visit, the subject 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.

Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigative product (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the Post-Titration Assessment visits (for titration prior to or at the

subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.

To be eligible for a dose up-titration:

- Subjects 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.
- There must be no clinically significant increase (as determined by the Investigator) in the subject's liver function tests.

7.5. 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). Child Pugh Scores should only be applied in patients who have evidence of cirrhosis at screening or demonstrate evidence of cirrhosis at screening or progression to cirrhosis during the study based on criteria presented in Section 7.5.4. 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 the assessments of signs and symptoms of hepatic injury and liver biochemistry, the investigational product may be interrupted or discontinued per criteria discussed in Section 7.5.2 and Section 7.5.3, and close monitoring procedures will be implemented (Section 7.7).

7.5.1. Signs and Symptoms of Hepatic Injury or Decompensation

Subjects 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: eg, 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: eg, confusion, swelling of the legs or abdomen
- Non-specific signs and symptoms of impaired health: eg, 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 subject 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 7.5.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.5 (3) triggering of investigational product interruption or discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 12.1.5.1 and Section 12.1.5.2), and (5) contact with the Medical Monitor.

7.5.2. Liver Biochemistry Assessments for Suspected Hepatic Injury or Potential Hepatic Decompensation

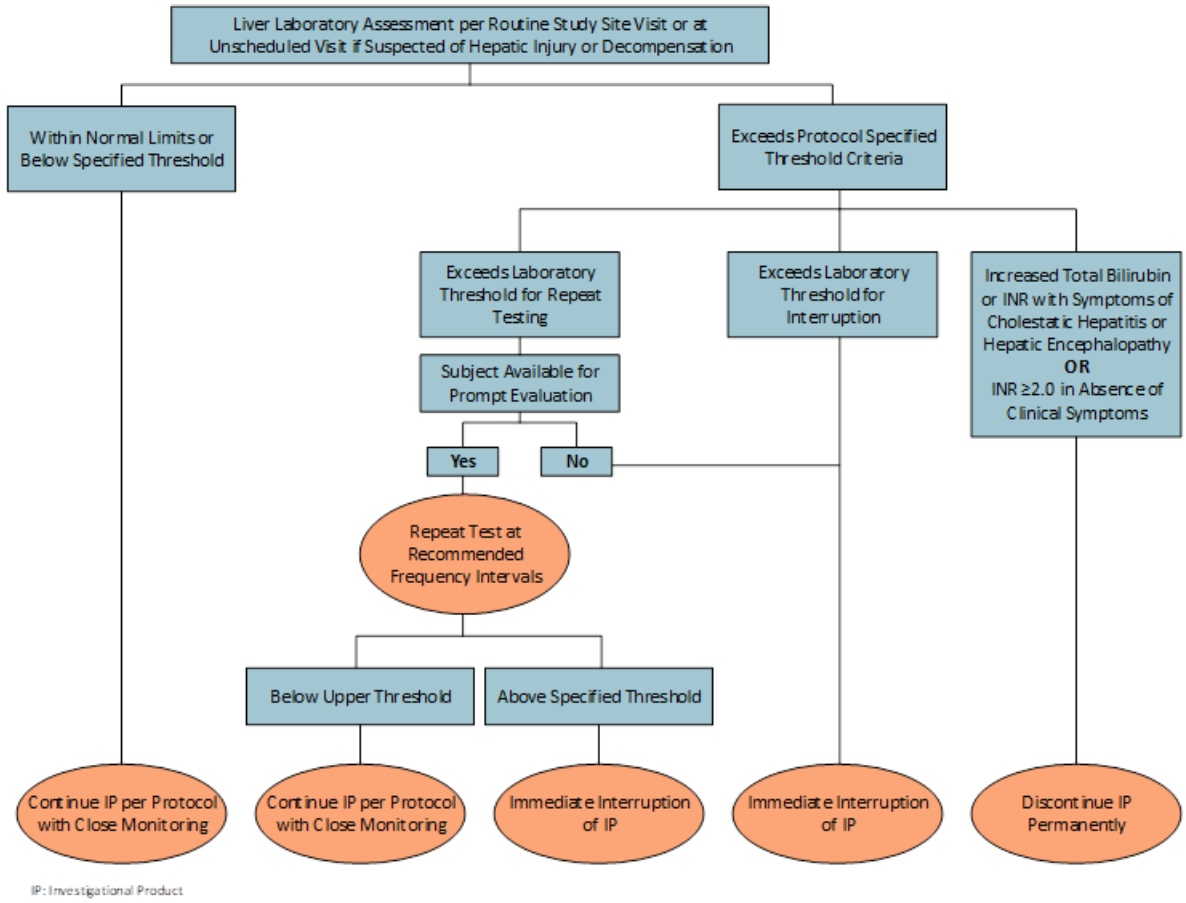
Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of subjects for potential hepatic injury or hepatic decompensation. These assessments will be performed at:

- 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 subject 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 subject evaluation (depending on the repeat result) are summarized in Table 4.

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 4: 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 subject 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 threshold	
B. 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 subject 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]		
>0.3unit increase from baseline	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt IP.	The subject 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 subjects 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 subjects' 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.

7.5.3. Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events

Subjects will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for the monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 5.

Investigational product should be discontinued permanently if the subject received a liver transplant or experiences multi-organ failure as defined in Table 5, Part A). Subjects should continue to return for scheduled study visits for safety follow up.

Subjects who experience other potential hepatic decompensation events defined in Table 5, Part B should be closely monitored until normalization or stabilization. Subjects may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.

Table 5: 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 4, 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.

7.5.4. Assessing Cirrhosis

7.5.4.1. Determination for Dosing Regimen

To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of determining dosing is defined as a

subject who has documented evidence or presence of one or more of the following cirrhosis indicators:

Biopsy results consistent with PBC Stage 4 (Ludwig 1978)

- TE 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)

Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A and Section 7.3).

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

7.5.4.2. Progression to Cirrhosis

When a subject identified as noncirrhotic at Baseline per the criteria listed in Section 7.5.4 exhibits any signs or symptoms associated with progression to cirrhosis, as defined by the same criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy (centrally read) unless not medically indicated. Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis.

Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.

Sites participating in the paired biopsy substudy must confirm progression to cirrhosis by biopsy as per the information outlined in protocol Addendum 2.

All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.

7.5.5. Child-Pugh Score

Child-Pugh (CP) 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 6 and can range from 5-15. Although CP score calculation will automatically be computed in all subjects, it should only be applied to subjects who meet criteria for progression to cirrhosis. Dose adjustment or discontinuation should not be considered based solely on the CP score, in subjects who do not meet criteria for presence of cirrhosis.

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). Sponsor 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 6: 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]		No	Grade 1 or 2	Grade 3 or 4

INR = international normalized ratio

[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
Child-Pugh criteria: Pugh 1973, Lucey 1997, Vilstrup 2014.

7.5.5.1. Mayo Risk Score

Mayo Risk Score (MRS) (Dickson 1989) is calculated and reported within the EDC system based on data entered into the eCRF. Calculation of MRS includes Investigator assessment of peripheral edema and the use of diuretic therapy, which will be assessed during adverse event and concomitant medicine review at the scheduled visits and entered into the eCRF, as well as total bilirubin, albumin, and prothrombin time results obtained from the central laboratory data.

7.6. 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 7), investigational product should be initiated at a lower dose and subjects 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 7. Subjects that 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 terminate at the time when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Table 7, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.

Table 7: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge

DOSE ADJUSTMENT		
Criteria	**Action Taken with IP**	**Adjustment**
Progress to cirrhosis and have CP A cirrhosis (CP score <7)	Adjust to a maximum daily dose of 10 mg (or equivalent placebo) in a blinded fashion	Not applicable. Remain at maximum daily dose of 10 mg (or equivalent placebo) for remainder of study.
Progress to CP B or C cirrhosis (CP score ≥7)	Adjust IP dose to 5 mg once weekly, then titrate to a maximum 10 mg twice weekly (at least 3 days apart).	After a minimum of 3 months, if at a lower dose, subjects may titrate to a maximum IP dose of 10 mg twice weekly per Investigator discretion.
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 4)[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 4[d]	Interrupt after confirmation by repeat testing	

Liver biochemistries indicative of potential hepatic decompensation in the absence of symptoms (see Part B of Table 4)[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 5)	Closely monitor until normalization	The subject 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	
Pregnancy	Interrupt	Patient should continue with the study visit schedule. The subject may re-start IP when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor
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)	Discontinue / No Rechallenge	Discontinue IP permanently and continue to return for scheduled study visits for safety follow up. Monitor closely for clinical outcomes per protocol. 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 4) are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy[f]		
Multi-Organ failure requiring hospitalization		
Liver transplantation		

Fully resolved = Return to baseline levels or return to within normal limits (WNL). IP = investigational product

[a] If subject 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 Postbaseline ≥3x baseline, Baseline >ULN and Postbaseline ≥2x Baseline, ALT or AST >3x baseline (and >ULN)

[d] ALT or AST ≥2x baseline, albumin <3.2 g/L or electrolytes (sodium <130 mEq/L).

[e] Conjugated bilirubin >0.5 mg/dL increase from baseline; 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 conjugated bilirubin 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.

[g] Multi organ failure including hepatorenal syndrome Type 1 or Type 2 and acute kidney injury, hepatopulmonary syndrome, or portopulmonary syndrome.

7.7. Close Observation

If investigational product is interrupted or discontinued as described in Section 7.6, subjects 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 subject 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 subject 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 subject 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 7.5.1, Section 7.5.2, and Section 7.5.3. These cases need to be discussed with the Sponsor's medical monitor:

- Repeating liver enzyme and serum bilirubin tests as described in Section 7.5.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject 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 subject 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 (HEV) when assessing for hepatic decompensation as infection with HEV 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

7.8. Criteria for Study Termination

The Sponsor 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 DMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 127 adjudicated events will have been accrued.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.
2. A mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN
3. Age ≥18 years

4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects of child-bearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
   - Intrauterine device (IUD)
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence, if in line with the preferred and usual lifestyle of the subject
6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     – Variceal bleed
     – Uncontrolled ascites
     – Encephalopathy

  - Spontaneous bacterial peritonitis
- Known or suspected hepatocellular carcinoma
- Prior transjugular intrahepatic portosystemic shunt procedure
- Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)

3. Mean total bilirubin >5x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
14. UDCA naïve (unless contraindicated)

8.4. Subject Withdrawal Criteria

Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. See Section 7.6 for withdrawal criteria related to potential hepatic injury and/or decompensation including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.1 below.

8.4.1. Other Reasons for Discontinuation of Study or Investigational Product

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

- Subject begins treatment with commercially available OCA
- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- 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 subject 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 subject withdraws consent (See Section 9.7.15).

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

8.4.2. Withdrawal of Consent

If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).

8.4.3. Lost to Follow-up

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

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject 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 CRF.

8.4.4. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.15, Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or matching 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 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, up to once daily, for the duration of the study.

All subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Drug Interactions

Subjects 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 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 Investigator's Brochure (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 with OCA that may be observed in study subjects.

PBC-Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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. Subjects who initiate commercial OCA therapy must discontinue investigative product and are expected to continue through the end of the study (see Section 9.7.15). The study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (see Section 9.7.15).

9.3. Treatment Compliance

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

Subjects should be instructed to complete a dosing diary to help monitor compliance to the prescribed dosing regimen. Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable,

follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to one of two treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will also serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2 below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects 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 subject). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the subject'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 subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The Data Monitoring Committee (DMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded subject data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the trial 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 Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0.

The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening Visit 1 interval is 3 to 8 weeks prior to Day 0. Screening Visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window. See Section 9.7.3 for scenario specific visit windows that may be applicable at Screening.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Month 1	±1 week (7 days)
Titration Visit – Standard Dosing Regimen	≥Month 3
Titration Visit 1 – Modified Dosing Regimen	≥Month 3
Titration Visit 2 – Modified Dosing Regimen	≥6 weeks after Titration Visit 1

Visit or Procedure	Visit Window and/or Interval
Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY)	≥6 weeks after Titration Visit 2
Post-Titration Visit	1 month and 2 months (±1 week [7 days]) from date of titration
Month 3 to Month 12	±2 weeks (14 days)
Quarterly visits (Months 15 to EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues investigative product at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues investigative product but continues in the study.

EOS = end of study; EOT = end of treatment

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of / study to the subject and will provide his/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 week to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 3 weeks to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 week to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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.

Collection of 2 serum chemistry samples (collected at least 2 weeks apart) during Screening is required for confirmation of the pretreatment serum chemistry values, including ALP and total bilirubin used to determine eligibility:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤5x ULN and/or an ALP >3x ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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
- Assess for the presence/absence of cirrhosis.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.

- Perform an ultrasound for HCC surveillance and gallbladder assessment (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 3 months of the planned Day 0 visit, and a report/adequate data are available, a pretreatment ultrasound is not required. If the ultrasound cannot be performed at Screening Visit 2 (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 must be reviewed to assess possible exclusion criteria prior to randomization.
- Assess and record any pretreatment-emergent AEs.
- Review and record prior and concomitant medications.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate. In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.

9.7.4. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to Fibroscan® TE device. If TE has been done within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc), the procedure may be completed within the screening visit window, at Screening Visit 1 (if data is needed for cirrhosis assessment) or as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
- Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where the device is available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data

are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.

  - Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.

- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- Review and record any nonstudy 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 subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- If hepatobiliary ultrasound for HCC screening and gallbladder assessment was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF])
  - Genetics (see Section 11.1.2.3)
- Perform assessments for calculation of Child-Pugh Score.
- Access the IWRS and dispense investigational product.
- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.

- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.5. Months 1, 2 Procedures

- Perform a physical examination.
- Assess and record AEs
- Review and record prior and concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 and Month 2 visit laboratory requirements:
  - At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Month 1 and Month 2 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern. The subject must also be contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;

  - A physical examination should be performed at the Month 3 visit if an onsite Month 1 or Month 2 visit was not performed.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Post-Titration Visit Procedures

- Perform a physical examination.
- Assess and record AEs.
- Review and record prior and concomitant medications
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration laboratory requirements:
  - At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration Visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern. The subject must also be contacted via telephone at the Post-Titration Visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;
  - A physical examination should be performed at the next scheduled visit if an onsite Post-Titration Visit was not performed
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 6 Procedures

- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject questionnaires (see Section 12.2.5)
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
- Provide the subject with a dosing diary to document his or her dosing.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.9. Month 9 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- PK assessment in participating subjects at select study sites (see Section 9.7.10).
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule.

Following collection of the Month 9 fasted samples (refer to Section 9.7.9, subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigative product and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigative product (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4-hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink with no other food allowed until after the final 6-hour post-dose sample is collected. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.11. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessments for calculation of Child-Pugh Score
- Review progression to cirrhosis algorithm
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires and (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to the Fibroscan® TE device.

- Perform an endoscopy (at all study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 and Month 9 Continued Follow-Up Procedures (±2 weeks)

- Perform assessments for calculation of Child-Pugh Score.

- Review progression to cirrhosis algorithm
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.13. Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.5)
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.

- Review and record prior and concomitant medications
- Review and record any nonstudy 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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

9.7.14. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to the Fibroscan® TE device.

- Perform an endoscopy (at all study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications
- Review and record any nonstudy 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.15. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 8) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject 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 and EOS procedures in the CRF.

Table 8: 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 IP	
Treatment Discontinuation[b]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[c]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[c]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	

Table 8: Early Discontinuation Scenarios (Continued)

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product
[a] Refer to Section 7.1.2 Schedule of Study Procedures, Table 2 for all procedures and evaluations required at the End of Treatment and End of Study Visits.
[b] Includes initiation of commercially available OCA.
[c] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. Additional data such as information on concurrent medical conditions, co-morbidities, relevant adverse events, and concomitant medications may be collected to help facilitate adjudication of these post-study events.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Review progression to cirrhosis algorithm
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).

- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- Review and record any nonstudy 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 accountability, and review dosing diary with the subject; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)

9.7.16. 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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin is observed during the course of the study, refer to Section 7.5 to confirm whether an unscheduled safety visit is required.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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 trial sites in support of clinical study 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 Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- 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 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Individual components of the primary endpoint
- Liver-related death
- Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.

  - Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in Addendum 2).

- HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.
- Liver biochemistry (see Table 12 for list of analytes to be tested)
- Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ELF, and Fibroscan (and others as determined during the course of the study).
- Clinical outcomes, including individual component of the primary endpoint (where available), liver transplant, and death will be compared to historical controls.
- PK of OCA and its conjugates.
- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Noninvasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other Secondary Assessments

- OCA (OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide) and C4 will be assayed to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
- Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Section 12.1.6 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 13.4) 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 suspected unexpected serious adverse reaction (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 13.4.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definitions of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE.

Subjects should be questioned in a general way, without leading the subject 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.

Subjects 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 whites of eyes, and bruising easily.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.1.4. Adverse Events of Special Interest

The following decompensation events are adverse events of special interest. A subset of these events are also individual components of the primary endpoint (Section 11.1.1).

- 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, 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

12.1.2. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Relationship of Adverse Events to Liver Biopsy

The Investigator will document her/his opinion of the relationship of an AE to liver biopsy using the criteria outlined in Table 10.

Table 10: Relationship of Adverse Events to Liver Biopsy

Relationship	Description
Related	A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.
Not Related	Any event that does not meet the above criteria.

12.1.4. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 11, must be entered on the AE CRF. 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 11: Severity of Adverse Events

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

12.1.5. Reporting of Adverse Events and Serious Adverse Events

12.1.5.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject'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.

In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any subject.

12.1.5.2. 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 be reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521

If an SAE is reported by email 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:

- Subject 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 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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

The Investigator is responsible for submitting information on 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, 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 12.1.6.

12.1.6. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition qualify as SAEs (see Section 12.1.1.2). The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.5.2). 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.

Given that the liver-related clinical outcome events may also meet the criteria of a SUSAR, but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data approximately quarterly, the Sponsor will not expeditiously report suspected liver-related 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 "study event" on the AE CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.

The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 or oesophageal varices haemorrhage), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological or clinical progression to cirrhosis (preferred term: hepatic cirrhosis).

12.1.7. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Medical Monitor, 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 subject 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.

12.1.8. 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 12.1.5.2.

SAEs that occur in subjects 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 12.1.5.2.

12.1.9. Notification of Poststudy 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 12.1.5.2.

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 12.1.5.2.

12.1.10. 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 subject 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 subject 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.

Drug-Induced Liver Injury or Disease Progression

All subjects 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 from drug-induced liver injury follow-up 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

At the time of consent for new subjects (or re-consent to the protocol amendments for ongoing subjects), subjects will 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. Subjects will 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 will be instructed to promptly bring subjects 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 will 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.

12.1.11. 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 7.6 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 sae@interceptpharma.com or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

The subject 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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 12.1.5 must also be followed.

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.2). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening Visit 1, Month 12, and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.2), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.6. Laboratory Assessments

Subjects will be instructed to attend any study or unscheduled laboratory visits (except Screening) in a fasted state, and subjects should remain fasted until their blood samples have been collected. At each visit, the Investigator or designee will verify that the subject has fasted for at least 8 hours and record fasting status in the source and CRF. If the subject reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.2). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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 12, and the normal reference ranges for liver biochemistries are shown in Appendix C.

Table 12: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low-density lipoprotein [VLDL] fractions and triglycerides[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	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Markers of Cholecystitis and Pancreatitis	amylase and lipase
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Other	OCA (parent and conjugates [glyco and tauro], OCA-glucuronide) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.11 through pregnancy outcome.

MELD scores and Child-Pugh score will be calculated at screening, and at all visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the first interim analysis, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK Population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8.

13.1.2. Determination of Sample Size

The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3× ULN. The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years of subject accrual and 6 years of follow up.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.
- A dropout rate of 10% is assumed

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

13.1.2.1. Sample Size Monitoring

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment

and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated quarterly in a blinded manner. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15

- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.10 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3). The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values as well as estimates of least-square means, standard errors, and 95% CIs will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time-to-event secondary efficacy analyses will compare OCA versus placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Progression to cirrhosis
- Time to occurrence of HCC
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as baseline TE, where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic (See Section 7.5.4). Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2).

Analyses of changes in MELD score, Child-Pugh score, MRS, IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.5.1. Association of Biochemistry with Clinical Outcomes and Clinical Benefit

The association between biochemistry including ALP and bilirubin with clinical outcomes will be assessed and the clinical benefit of OCA using biochemistry as a surrogate endpoint will be evaluated. Detailed analysis will be described in the SAP.

Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA using biochemistry as a surrogate endpoint for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67x ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76x ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, "where no obvious single optimal external control exists, it may be advisable to study multiple external controls". In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, which serves as an external control for supportive analysis.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is "similar" to a participating subject. The historical database control should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.3).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment between the treated subjects and the matched natural history subjects.

A full range of covariates across which the treatment and historical controls might differ will be considered to mitigate potential bias. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible. Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation, to avoid biased results that are in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.

A third-party statistician(s) will perform the propensity score modeling and matching. This third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses. Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, HCC, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)
- Time to liver transplant or liver-related death

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), using similar statistical methodology as specified above.

Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.

13.1.9. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below. In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.

13.1.9.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.9.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.9.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified timepoint for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.10. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however, hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.11. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. Subgroups will be assessed at Baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)

- Early (normal albumin and normal bilirubin)
- Moderate (abnormal albumin or abnormal bilirubin)
- Advanced (abnormal albumin and abnormal bilirubin)

The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.

- Monotherapy in patients who are intolerant or non-responsive to UDCA
- Elderly patients

Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.

Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.

13.1.12. Continuous Monitoring and Interim Analyses

Blinded safety reports including the accrual of events, drop outs, and/or loss of subjects to commercially available OCA will be reviewed by the DMC on a regular basis.

Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% (64 events) and 75% (96 events) of clinical outcome events, respectively.

The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy)

of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

Adverse events of special interest as described in Section 12.1.1.4 will be summarized for each treatment group. In addition, each event is a component of the primary endpoint, and will be summarized as secondary endpoints as described in Section 13.1.4.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

13.2.4. Cardiovascular Adjudication Committee

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).

13.3. 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 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 subjects. 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 subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (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 subject safety, which alter the conduct of this study. The Investigators will inform the subjects of such actions and the protocol, patient information sheet (PIS), and consent will be revised, as appropriate.

13.4. Adjudication Committees

All suspected liver-related clinical outcomes, and MACE/Expanded MACE, 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 2 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

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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. 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.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 Medical Monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, 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 (when available) 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: The Sponsor, 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.

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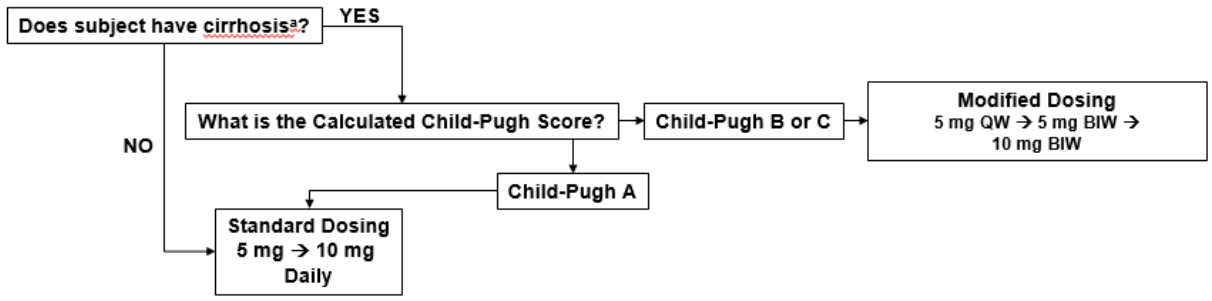
APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT

Subjects with cirrhosis and classified as Child-Pugh B or Child-Pugh C at Screening will follow a modified dosing schedule initiating 5 mg OCA or matching placebo once weekly as described in Figure 3. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly (Table 13).

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Figure 3: Dosing by Cirrhosis Status and Child-Pugh Score



[a] Cirrhosis may be assessed by histology or non-histological methods as defined in Section 7.5.4.
BIW = twice weekly; QW = once weekly

Table 13: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Modified Dosing Regimen for Child-Pugh B or Child-Pugh C
Starting Dose [a] (Day 0)	5 mg once weekly
Titration 1 [b] (≥Month 3)	5 mg twice weekly[c]
Titration 2 [b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]

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

Dose Titration due to Change in Cirrhosis or Child-Pugh Score

When subjects demonstrate a change in cirrhosis status (as assessed per Section 7.5.4) or Child-Pugh Score (Section 7.5.5 dosing should be reassessed and the dosing regimen modified appropriately. Changes in Child-Pugh Score that result from a transient, explainable change in

laboratory parameters (eg, increase in INR due to vitamin K deficiency) should be documented appropriately and discussed with the Medical Monitor before any continuation or change to the dosing regimen.

Possible scenarios for dosing modifications include:

- Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C
- Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study

Subjects may titrate dose and dosing frequency up or down as appropriate, within the dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month and 2-Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.7).

Unscheduled Titration Visit, Optional Visit

An unscheduled up-titration visit may be scheduled for as early as 6 weeks after the initial titration visit (or subsequent titration visit) occurs for subjects who are following the modified dosing regimen. The visit procedures required for the unscheduled titration visit are outlined below. Subjects who up titrate at an unscheduled visit will continue to follow the regular visit schedule for all other study visits.

For subjects who up titrate at an unscheduled visit the following procedures will be performed:

- Assess and record AEs.
- Review and record concomitant medications.
- Perform the pre-Titration Tolerability Assessment as outlined in Section 7.4.1.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

For subjects who up-titrate at an unscheduled visit: The ±1-week window related to the 2-month Post-Titration Visit can be modified to occur 2 weeks earlier or 2 weeks outside of the allowed visit window to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the 2-month Post-Titration Visit is performed during a regularly scheduled study visit, all scheduled procedures associated with that visit should be performed.

APPENDIX B. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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Online-Only Content: Audio podcast is available at www.jama.com.

APPENDIX C. REFERENCE LABORATORY VALUES FROM CENTRAL LABORATORIES

Covance Central Laboratories (Indianapolis, Indiana, US [for North America and Latin America regions]; Geneva, Switzerland [for Europe]; and Singapore [for Asia-Pacific region]) will serve as the central labs for analysis or specimen management for the analytes listed in the Table 12 of Protocol 747-302 Version 4. The following in text table provides the Covance Laboratory reference ranges for the pertinent liver biochemistries analyzed by Covance. These reference ranges are sex and/or age specific, and can change during the course of the clinical trial; therefore, investigative sites should always refer to the reference ranges available on the Covance issued laboratory reports.

		Covance Indianapolis		Covance Geneva and Covance Singapore	
Analyte	Sex	Age[a]	Reference Range	Age[a]	Reference Range
Albumin	Both	18Y – 69Y	SI Units: 33-49 g/L Conventional Units: 3.3-4.9 g/dL	18Y – 69Y	33-49 g/L
		69Y-80Y	SI Units: 33-46 g/L Conventional Units: 3.3-4.6 g/dL	69Y-80Y	33-46 g/L
		80Y-150Y	SI Units: 30-46 g/L Conventional Units: 3.0-4.6 g/dL	80Y-150Y	30-46 g/L
ALP	Female	18Y - 50Y	31-106 U/L	18Y - 50Y	31-106 U/L
		50Y - 60Y	35-123 U/L	50Y - 60Y	35-123 U/L
		60Y - 70Y	35-123 U/L	60Y - 70Y	35-123 U/L
		70Y - 80Y	35-123 U/L	70Y - 80Y	35-123 U/L
		80Y - 90Y	35–135 U/L	80Y - 90Y	35–135 U/L
		90Y – 150Y	35-140 U/L	90Y – 150Y	35-140 U/L
ALP	Male	18Y - 50Y	31-129 U/L	18Y - 50Y	31-129 U/L
		50Y - 60Y	35-131 U/L	50Y - 60Y	35-131 U/L
		60Y - 70Y	35-125 U/L	60Y - 70Y	35-125 U/L

		Covance Indianapolis		Covance Geneva and Covance Singapore	
Analyte	Sex	Age[a]	Reference Range	Age[a]	Reference Range
		70Y - 80Y	35-130 U/L	70Y - 80Y	35-130 U/L
		80Y - 90Y	35–125 U/L	80Y - 90Y	35–125 U/L
		90Y – 150Y	35-125 U/L	90Y – 150Y	35-125 U/L
ALT	Female	18Y – 69Y	6-34 U/L	18Y – 69Y	6-34 U/L
		69Y – 150Y	6-32 U/L	69Y – 150Y	6-32 U/L
ALT	Male	18Y – 69Y	6-43 U/L	18Y – 69Y	6-43 U/L
		69Y – 150Y	6-35 U/L	69Y – 150Y	6-35 U/L
AST	Female	18Y – 59Y	9-34 U/L	18Y – 59Y	9-34 U/L
		59Y – 150Y	9-34 U/L	59Y – 150Y	9-34 U/L
AST	Male	18Y – 59Y	11-36 U/L	18Y – 59Y	11-36 U/L
		59Y – 150Y	11-36 U/L	59Y – 150Y	11-36 U/L
Direct Bilirubin	Both	18Y – 150Y	SI Units: 2-7 umol/L Conventional Units: 0.1-0.4 mg/dL	18Y – 150Y	2-7 umol/L
Indirect Bilirubin	Both	0Y – 150Y	SI Units: 0-21 umol/L Conventional Units: 0.0-1.2 mg/dL	0Y – 150Y	0-21 umol/L
Total Bilirubin	Both	18Y – 150Y	SI Units: 3-21 umol/L Conventional Units: 0.2-1.2 mg/dL	18Y – 150Y	3-21 umol/L

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Y = years; SI=International System of Units

[a] The unstated word "to" is implied by the "dash" appearing in age specific reference ranges. A range such as "0-59 years" and "59-150 years" means: "0 up to but not including 59 years" and "59 up to but not including 150 years".

Source: Covance Laboratory Services Manual Version 5.0.0. Dates vary by region: 10 Nov 2016 (North America), 22 Nov 2016 (Europe and Singapore)

APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

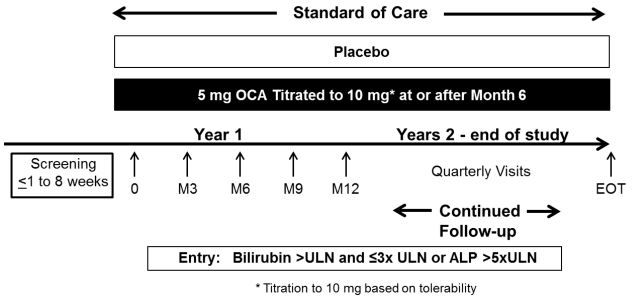
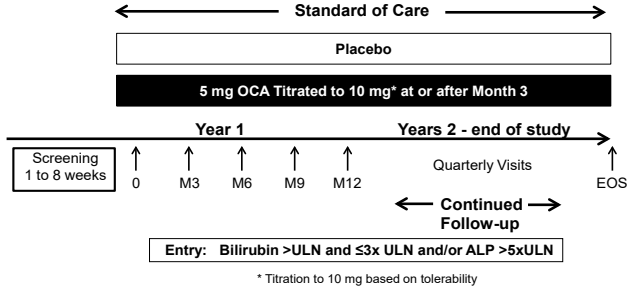
Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: 29 April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact**:** PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD	Contact**:** PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP)	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP)

Section	Original Text	Revised Text
	and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Section	Original Text	Revised Text
Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5×ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and/**or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12.	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>3. Mean total bilirubin >3× ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

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5. Deleted text</td></tr>
<tr><td>Synopsis</td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td>Statistical Methods: Other Efficacy Analyses
• Added text</td><td>Statistical Methods: Other Efficacy Analyses
• Development of varix/varices</td></tr>
<tr><td>4</td><td>List of Abbreviations
Added text</td><td>List of Abbreviations<table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC.</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment.</td></tr>
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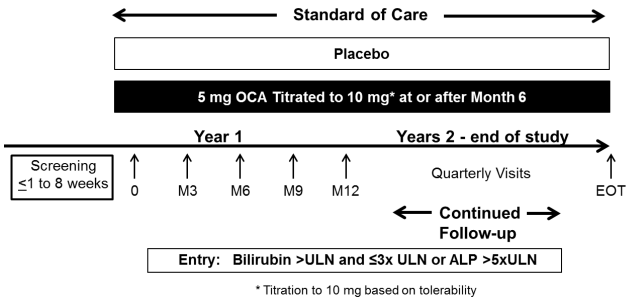
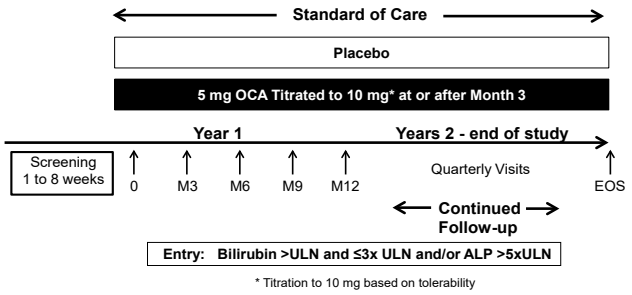
Section	Original Text	Revised Text
	The LTSE phases of both Phase 2 studies and the Phase 3 study support the long-term safety of OCA and demonstrate a durable therapeutic response **up to 4 years.** The **LSTE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete	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**.** The **LTSE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete
5.5.2.1	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.

Section	Original Text	Revised Text
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.**
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….

Section	Original Text	Revised Text
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)*** ***Visit Window ≤1 to 8 wks …*** ***Visit window in 2nd column added new text*** ***Added text*** *Footnote a:* All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on**	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now **"Screening Visit 1"*** *2nd column now **Screening Visit 2*** ***3** to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3*** *Footnote a* All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both**

Section	Original Text	Revised Text
	ALP (ALP >5× ULN), the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3× ULN).**	**analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**.
	Footnote b: The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed	*Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(± 1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.
	Footnote e: Medical history at Screening will smoking and alcohol consumption history and current habits for both.	*Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both.
	Footnote g: **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1)	*Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6)
	Footnote h: Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.	*Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	*Footnote i: **Added text***	*Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote j: ***Added text***	*Footnote j*: **Ultrasound will be conducted to enhanced HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	*Footnote k***: *Added text***	*Footnote k:* **Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central**

Section	Original Text	Revised Text
		laboratory evaluations per the Child-Pugh scoring system noted in the case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
	Footnote l: ***Added text***	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
	Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change	***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***
7.3	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched

Section	Original Text	Revised Text
	placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5× ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and/**or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile),

Section	Original Text	Revised Text
	contraception during the study and for 30 days after the end of treatment visit.	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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** 4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3× ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**

Section	Original Text	Revised Text
	5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	**5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent. The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text***	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures)**. The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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 potential adjudicated hepatic and/or cardiovascular events**

Section	Original Text	Revised Text
	The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	Concomitant Medications 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 CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to**

Section	Original Text	Revised Text
		continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.
9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for**

Section	Original Text	Revised Text
		the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding. **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.**
9.6	Restrictions **No additional restrictions.**	Restrictions **Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment
</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
<tr><td>EOS
(When subject terminates the study)</td><td>The final study visit; EOS will occur concurrent with EOT if a subject discontinues investigative product at the time the subject’s</td></tr>
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Section	Original Text	Revised Text
		participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues investigative product but continues in the study. EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**. • For subjects that do not qualify based on ALP alone (ALP >5×	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart • For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of **all available (at least 2;**

Section	Original Text	Revised Text
	ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).	**including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs** • **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours**

Section	Original Text	Revised Text
		– **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits** • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**

Section	Original Text	Revised Text
	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• *Added text*	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are <150 × 10^9 /L.**

Section	Original Text	Revised Text
	• ***Added text***	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• ***Added text***	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**
9.7.6	Month 3 Procedures • ***Added text*** • ***Added text***	Month 3 Procedures • **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:**

Section	Original Text	Revised Text
		– **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • ***Added text***	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • ***Added text***	Month 9 Procedures • **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**
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water.	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.12), subjects who are participating in the PK assessment will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water.

Section	Original Text	Revised Text
	Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**

Section	Original Text	Revised Text
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**

Section	Original Text	Revised Text
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will

Section	Original Text	Revised Text
		only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.**
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
		[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7.
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.	Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing
	Prior to the EOT Visit:	Prior to the EOT/**EOS** Visit:
	During the EOT Visit: • Subject questionnaires (see Section 12.2.6) • Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable	During the EOT/**EOS** Visit • Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)** • Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
	• ***Added text***	• Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6)
	• ***Added text***	• Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months)
	• ***Added text***	• Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• ***Added text***	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline**

Section	Original Text	Revised Text
		(and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of

Section	Original Text	Revised Text
	• ***Added text***	outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:** **a. PBC-40: The PBC-40 (Jacoby 2005) 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.** **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).**

Section	Original Text	Revised Text
		c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
12.1.1.2	Serious Adverse Event • ***Added text***	Serious Adverse Event **Events <u>not</u> 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**

Section	Original Text	Revised Text
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Section	Original Text	Revised Text
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued investigative product, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with investigative product, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to Appendix C)** and the Sponsor's policies.
19	List of References • Added text	List of References Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36. Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629. Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 (DATED 12 NOV 2015)

Rationale

The changes to Amendment 1 of the protocol, detailed below, generated specifically for regulatory authority requests, include an additional exclusion criteria and changes to text precluding UDCA naïve subjects from entering the study and clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, thus answering questions raised by regulatory authorities.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1.1. (Note: Revised text in Amendment 1.1 is indicated in bold font, and the text deleted from Protocol Amendment 1 is crossed out in the table below. Minor formatting changes are not listed.)

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
Title Page	Original: 03 October 2014 Amendment 1: 29 APRIL 2015	Original: 03 October 2014 Amendment 1: 29 **April** 2015 **Amendment 1.1: 12 November 2015**
Study Personnel Contact Information	~~Mobile: PPD (Pacific time zone)~~ Telephone: PPD ~~Telephone~~ PPD	(deleted) Telephone: PPD (deleted)
Synopsis, Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
Synopsis, Statistical Methods: Sample Size Justification	• ~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)
8.3 Subject Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
9.2 Concomitant Medications	(insertion)	**The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile**

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
		of caffeine, a sensitive CYP1A2 substrate, 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.
12.1.4.2 Reporting of Serious Adverse Event	~~Mobile: PPD (Pacific time zone)~~ Telephone: +1 ~~858 964 1571~~	(deleted) Telephone: PPD
13.1.2 Determination of Sample Size	~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)

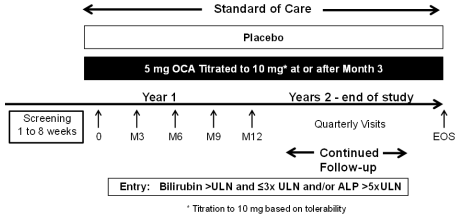
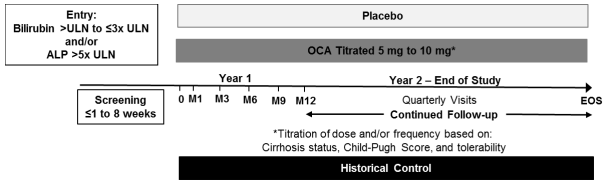
APPENDIX F. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 TO VERSION 3 (DATED 07 SEP 2016)

Rationale

The changes to Version 3 of the protocol, include dosing adjustments based on Child-Pugh scoring, additional exclusion criteria, changes to text precluding UDCA-naïve subjects from entering the study.

Please note that the Sponsor has renamed protocol "amendments" to "versions", therefore all future revisions that require a revised protocol will have an associated "version" number. The table below includes substantial revisions made to Protocol 747-302 under Version 3, which encompass the revisions captured in Protocol Amendment 1.1. Revised text in Version 3 is indicated in bold font, and the text deleted from Protocol Amendment 1.1 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 (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	... ~~Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups.~~ The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. ~~Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.~~	... Investigational product will be taken orally, once daily **for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C.** The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).	To incorporate a dosing and titration regimen based on subject's Child-Pugh Scores, to align with the recommended dosing regimen found in the Ocaliva US Package Insert for patients with hepatic impairment.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology. 7.1.1, Study Design Diagram, Figure 1	Schematic diagram 	Updated schematic diagram  **Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration**	Incorporate updated dosing scheme to reflect addition of Child-Pugh scoring.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	(insertion)	**Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:** • **Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.** • **For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.** • **Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability.** **Includes New Table: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Revised methodology to incorporate the changes in dosing for subjects based on the Child-Pugh Scores.
5.1, Overview	(insertion)	**The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication**.	Language updated as OCA is approved in the US with the trade name Ocaliva.

5.5.2.2, Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment	(Insertion)	**New section: Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment** **Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses and those from bile acids in the literature suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.** **Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose**	Provide the rationale to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores into the protocol.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		(full modified dosing regimen is described in Appendix A).	
5.6, Summary of Known Potential Risks with OCA	(Insertion)	**…These findings were seen more frequently with doses above 10 mg OCA. In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.**	Added two AE terms reported in the updated Investigator's Brochure.
7.1, Overall Study Design	…~~Investigational product will be initiated at 5 mg OCA or matched placebo.~~ Following 3 months of treatment with investigational product, ~~subjects~~ should be titrated ~~in a blinded manner (ie, subjects randomized to OCA will increase their dose to~~ 10 mg OCA) based on tolerability	Investigational product will be taken orally, once daily**. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo.** Following 3 months of **once daily** treatment with investigational product, **the dose** should be titrated **to a maximum** 10 mg OCA **or matching placebo once daily**, based on tolerability (see Section 7.3). **Subjects with cirrhosis and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.**	Amend the protocol to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores.
7.1.2, Table 1, Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2), 9.3, Treatment compliance	~~Safety Contact~~	This visit has been deleted.	Replaced with the 1 Month Post-Titration Visit.
	(Insertion)	Added the following visits: • Month 1 • 1 Month Post-Titration Visit	Visits were added to accommodate the updated dosing and titration regimen based on subject's Child-Pugh Scores.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	[b]~~The subject should be contacted by telephone on a monthly basis in between at clinic study visits at Month 1 and Month 2 (± 1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.~~ [e]~~As soon as possible upon study discontinuation and as near as possible to last dose taken.~~ [n]~~Subject to begin dosing on Day 1~~	Deleted.	Result of table being updated for the dosing and titration regimen based on subject's Child-Pugh Scores.
	(Insertion)	Added the following study procedures: • Cirrhosis Status Assessment[e] • Assessments for Child-Pugh Scores[g] • Dose Titration: Standard Dosing[n,o] • Dose Titration: Modified Dosing [n,o] • Dosing Diary	Study procedures were added to accommodate the updated dosing/titration regimen. Dosing diary was added to improve compliance.

	(Insertion)	Added the following footnotes: • **[b]Safety Post-Titration visits must be performed 1 month + 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.** • **[c]Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.** • **[f]Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.** • **[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.** • **[n]Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.** • **[o]Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh score (Section 7.3). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for**	Added footnotes provide clarity regarding assessments and visits based on the evaluation of Child-Pugh scores.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A. • **[p]Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet**.	
7.1.2, Table 2, Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)		**New table- Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)**	Divided Schedule of Study Procedures into 2 tables, updated to include visits added per updated dosing/titration information.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.3, Planned Dosing Regimen	7.3 ~~Treatment Assignment~~ ~~Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3-month study visit or at any study visit thereafter depending on tolerability.~~	**7.3 Planned Dosing Regimen** Subjects will **be randomized to treatment with** either **OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.** **Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).** **For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.**	Section renamed to reflect changes in titration and dosing for subjects with hepatic impairment.
	(Insertion)	**New: Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Tables added to clarify changes in titration and dosing.
		New: Table 4: Determination of Dosing Regimen	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.4 Dose Titration Criteria	~~After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA~~ or ~~matched placebo (in a blinded manner) at the 3-month visit or any study visit following the 3-month visit based on~~ tolerability ~~of investigational product~~. ~~For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10 mg dose if tolerated~~	**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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh Score.** **Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.** **Tolerability Dose Titration - Investigators** may decrease **the dosing frequency** or dose **for any subject** at any time during the study, as considered **clinically** appropriate (eg, tolerability; **see Section 7.4.2).** **Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due** to **changes in cirrhosis or Child-Pugh 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.**	Entire section revised to reflect changes in titration and dosing.
7.4 Dose Titration Criteria	(Insertion)	**New: Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score**	

7.4 Dose Titration Criteria	(Insertion)	**Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).** **Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).** **Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.** **Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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 and table added to provide dosing guidelines to investigators.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.4.1, Pre-Titration Tolerability Assessment Requirements	(Insertion)	**7.4.1 Pre-Titration Assessment Requirements** **Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigative product (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.** **To be eligible for a dose up-titration:** **• Subjects 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.** **• There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required**	Section added to provide guidance for assessing subject tolerability prior to titration.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
8.4.2, Other Reasons for Discontinuation of Study or Investigational Product	(Insertion)	• **Subject begins treatment with commercially available OCA** **… safety concerns and related to study drug** • Consent may be fully withdrawn **(in which case the subject discontinues both investigational product and study visits and procedures)** **…Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.**	Added text as Ocaliva is commercially available in the US and therefore subjects may be discontinued if they began off-study treatment with Ocaliva.
8.4.2.1, Elevated Liver Enzymes	(Insertion)	**New Section: 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.**	Section added to incorporate monitoring of liver test results during the study.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.1, Investigational Product Treatment Regimen	~~**9.1.1 Dose Adjustment Beginning at Month 3**~~ ~~After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted~~.	**At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.**	Section revised to reflect changes in titration and dosing.
9.2, Concomitant Medications	Subjects taking bile acid sequestrants (BAS) 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).	New sub-heading**:** ***Drug Interactions*** Subjects 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 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.** (…) **Information related to additional drug-drug interaction (DDI) studies is available in the current version of the Investigator's Brochure (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 with OCA that may be observed in study subjects.**	Section revised to provide additional information on drug-drug interactions with OCA.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.2.1, Prohibited Medications	… the Investigator should be cognizant of the possibility of double dosing ~~and encourage the discontinuation of open-label OCA therapy. However, if~~ commercial OCA therapy ~~remains, then investigational product should be discontinued to avoid potential double dosing~~. ~~Subjects that discontinue investigational product but continue commercial OCA therapy~~ are expected to continue through the end of the study, ~~and~~ the …	… the Investigator should be cognizant of the possibility of double dosing. **Subjects who continue with** commercial OCA therapy **must** discontinue **investigative product and** are expected to continue through the end of the study. …	Ocaliva is commercially available in the US and, therefore, subjects wishing to take commercially available drug are not discouraged, but they must discontinue investigative product.
9.7.1, Visit Windows	(insertion)	**Added the following visit windows:** • **Month 1 (+1 week [7 days])** • **Titration Visit – Standard Dosing Regimen (≥Month 3)** • **Titration Visit 1 – Modified Dosing Regimen (≥Month 3)** • **Titration Visit 2 – Modified Dosing Regimen (≥6 weeks after Titration Visit 1)** • **Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY) (≥6 weeks after Titration Visit 2)** • **Post-Titration Visit, (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency)**	Added visits to accommodate the updated dosing/titration scheme.

9.7.3, Assessing Cirrhosis	(Insertion)	**New: 9.7.3. Assessing Cirrhosis** **To determine which dosing regimen subjects should follow, the presence or absence of 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 is defined as a subject 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/mm3) with:** **– persistent decrease in serum albumin, or** **– elevation in prothrombin time /INR (not due to antithrombotic agent use), or** **– elevated bilirubin (2× ULN)** **Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A).** **Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in**	Added section to assess cirrhosis as this assessment will determine the acceptable dosing regimen based on a subject's Child-Pugh score.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		cirrhosis status will necessitate re-evaluation of the dosing regimen.	
9.7.4, Child-Pugh Score	(Insertion)	**9.7.4. Child-Pugh Score** **Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh 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.** **It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen**	Section added to provide Investigators with information on the Child-Pugh scoring system.
9.7.4, Child-Pugh Score	(Insertion)	**Table 6 (New) Child-Pugh Scoring System**	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.6, Screening Procedures (1 to 8 Weeks prior to Day 0)	(Insertion)	The following procedures were added: Screening Visit 1 procedures are as follows: • **Provide the subject with a dosing diary to document his or her dosing** • **Assess for the presence/absence of cirrhosis** • **Perform status assessment for calculation of Mayo Risk Score** Screening Visit 2 procedures are as follows: • **Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.**	Procedures added to assess cirrhosis.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.7, Day 0 Procedures (Randomization)	9.7.4. ~~Day 0 Procedures~~ ~~• Perform an ultrasound for hepatocellular carcinoma (HCC) surveillance (if equipment is unavailable, …~~ ~~• Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments.~~ ~~□ Presence/absence of peripheral edema~~ ~~□ Presence (degree)/absence of ascites~~ ~~□ Presence (degree)/absence of hepatic encephalopathy~~	9.7.**7**: Day 0 Procedures (Randomization) • **Provide the subject with a dosing diary to document his or her dosing.**	Updated visit to accommodate the updated dosing/titration scheme.
9.7.8, Month 1 Procedures	9.7.5 Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone])	9.7.**8** Month 1 Procedures • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:** - **At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, …** - **If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. …**	Revised section to include the new Month 1 visit procedures.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.9, Month 3 procedures, 9.7.11, Month 6 Procedures, 9.7.12, Month 9, 9.7.14, Month 12 Procedures	(Insertion)	• **Perform assessments for calculation of Child-Pugh Score**	Added procedure to accommodate the updated dosing/titration scheme.
9.7.9 thru 9.7.17	(Insertion)	**If up-titration will occur at this visit, complete the pre-titration visit and visit related assessments as outlined to ensure all procedures required for dose titration eligibility have been met, including the required review of the dose titration laboratory parameters.** • **Provide the subject with a dosing diary to document his or her dosing** • **… review dosing diary with the subject**	Text added to clarify procedures required before up-titration.

9.7.10, Post Titration Visit Procedures	(Insertion)	New**: 9.7.10. Post Titration Visit Procedures** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.** • **Obtain blood samples for serum chemistry, hematology, and coagulation tests.** • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration visit requirements:** **- At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.** **- If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review**	Added visit to accommodate the updated dosing/titration scheme.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		concomitant medications, and assess investigational product compliance. • **Schedule the next visit, reiterate dosing instructions, and advise the subject:** **- 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…**	
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	(Insertion)	**…Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule**.	Clarify that subjects with hepatic impairment may continue to participate in the PK assessment.
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink…	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink **with no other food allowed until after the final 6-hour post dose sample is collected…**	Clarify PK collection procedures.
11.1.2.2, Other Secondary Assessments	• OCA (~~and its conjugates~~) and C4 will be assayed	• OCA **(OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide)** and C4 will be assayed **to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified**.	Clarify the analytes to be measured for the PK analyses.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
11.1.2.4, Potential Clinical Outcome Events	(Insertion)	**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 13.4.**	Revised to clarify that potential clinical outcome events meeting the criteria of a SUSAR will not be reported to regulatory authorities expeditiously.

12.1.4.2 Reporting of Serious Adverse Event	In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the ~~medical monitor.~~ All SAEs ~~occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious)~~ must be reported to the ~~medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE~~. SAEs are reported by entering the SAE data into the ~~electronic data capture (EDC) system~~. Entering the SAE data into the EDC system will automatically notify the ~~medical monitor~~ of the event. In the event that the EDC system is inaccessible, an SAE may be reported by ~~telephone or fax~~ using a paper SAE Report form. 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: ~~subject~~ number and ~~initials, a description of the event~~, at least **one** criterion classifying the event as serious and the name and title of the reporting individual. ~~Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting~~ to regulatory authorities by the Sponsor or designee(s). ~~Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to~~	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 be reported by: • **E-mail to the SAE email address: sae@interceptpharma.com** • **Fax** using a paper SAE **report** form: **+1 800 497 8521** • **Telephone: +1 858 964 1571** 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: • **Subject** 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 Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) **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**	Updated guidance for reporting SAEs.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	~~+1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible~~. 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. ~~A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).~~ The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) ~~safety reports (SUSARs)~~ that occur during the study within the time frames required by each regulatory agency. ~~The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).~~ ~~Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities~~	**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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.** **The Investigator is responsible for submitting information on IND 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND 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 12.1.5.**	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Section 12.1.5, Suspected Liver-related Clinical Outcome Events	Clinical Outcome Events ~~(Appendix A) as well as Anticipated Events (Appendix B) will not undergo~~ expeditous reporting.	**12.1.5 Suspected Liver-Related Clinical Outcome Events** **Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.** **Given that the liver-related clinical outcome events could also meet the criteria of a SUSAR, please refer to Section 11.1.2.4.** **The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial and peritonitis (preferred term: peritonitis bacterial).**	Updated section to account for events related to hepatic impairment**.**

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
13.2.4, Cardiovascular Adjudication Committee	13.2.3 (…) In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study ~~and will be described separately~~.	**New Section: Cardiovascular Adjudication Committee** In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. **Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).**	Committee added to assess cardiovascular events in subjects during the study.

13.4, Adjudication Committee	All ~~potential endpoint events~~ will be reviewed by ~~an~~ adjudication committee before inclusion in the any analysis. The ~~adjudication of potential clinical endpoint~~ events will include, ~~but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership~~, the reporting of events by the study site, ~~reporting~~ of the ~~final assessment,~~ supply of source documentation to the committee, ~~the~~ review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members ~~will remain blinded to treatment group throughout the study~~. ~~In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.~~	All **suspected liver-related clinical outcomes, 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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific**	Committees added to assess liver impairment in subjects during the study.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.	
Appendix A, Modified Dosing Regimen for Subjects with Child-Pugh B/C Hepatic Impairment	(Insertion)	New**: APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT**	Added section to describe changes in dosing and titration for subjects assessed as cirrhotic Child-Pugh B or Child-Pugh C.
Appendix B, LIST OF STUDY 747-302 OUTCOME EVENTS	Was Appendix A	Now Appendix B	The hepatic dosing appendix became Appendix B
Appendix C	~~LIST OF STUDY 747-302 ANTICIPATED EVENTS~~	Deleted	Replaced by Appendix B, more comprehensive description of the outcome events.

APPENDIX G. SUMMARY OF CHANGES: PROTOCOL VERSION 3 TO PROTOCOL VERSION 3.1 (DATED 23 DEC 2016)

Please note that Protocol 747-302 Version 3.1 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. This summary of changes is provided for completeness. A full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided in Appendix I.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the expansion of the spectrum of stages of PBC disease, the addition of progression to cirrhosis as a secondary endpoint, and the addition of two interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

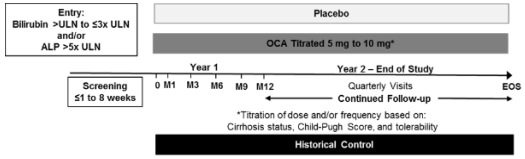
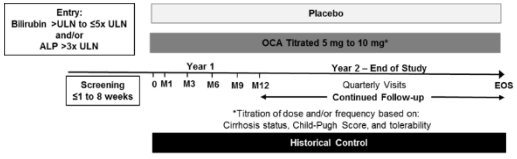
The following table includes revisions that were made to Protocol Version 3.1 with an associated reason or justification for the change. Rationales (Justifications for Change) that impact multiple sections are provided below and referenced in the table with the appropriate rationale number.

1. The phase of the study has been changed from '3b' to '4' to reflect that this is a post-marketing study.
2. The term 'primary biliary cirrhosis' has been changed to 'primary biliary cholangitis' throughout the document to reflect recent changes in nomenclature for PBC.
3. The increase in number of required events from 121 to 127 is due to the addition of two interim analyses (IA), which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy or futility) of the study. One IA will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). Inclusion of patients with earlier stage disease will also increase the time to event requiring more events in order to keep follow-up to approximately 6 years.
4. The first-year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by two years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.
5. 'Encephalopathy' has been modified to 'Hepatic Encephalopathy' to clarify that the relevant clinical outcome endpoint should be related to hepatic disease.

6. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of Hepatocellular Carcinoma.
7. **Broadening the Spectrum of Disease:** Lowering the minimum allowable baseline ALP to 3x ULN and raising the maximum allowable baseline total bilirubin to 5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the phase 3 protocol 747-301.
8. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
9. The increase in enrollment from 350 to 428 is due in part to the increased number of events, and in part due to the change in the estimated Placebo baseline hazard rate which resulted from changing the lower limit of ALP from 5× ULN to 3× ULN in the enrollment criteria #2.
10. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential non-invasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of 302.

The text deleted from Protocol Version 3 is crossed out while revised text in Version 3.1 is indicated in bold font in the table below. Minor/editorial changes and non-substantial changes are not listed individually in the summary table below.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	**Or if Not Available:** Contact: PPD **MD, PhD Medical Director, Clinical Research,** Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	Back-up medical monitor responsibilities were transferred to PPD
Synopsis, Studied Period (years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	~~3b~~	**4**	Rationale 1
Synopsis, Objectives, Primary, Statistical	• Encephalopathy (as defined by a West Haven score of ≥2) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5 Rationale 6

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis		• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities **unless confirmed by biopsy**	
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***Insertion*** To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects	**To assess the effect of OCA compared to placebo on progression to cirrhosis** To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 6
Synopsis, Methodology: Schematic Diagram Section 7.1.1 Study Design Diagram, Figure 1	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.	Rationale 7 Rationale 8

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (planned)	Approximately ~~350~~ subjects	Approximately **428** subjects	Rationale 9
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ≤~~3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 7
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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:	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below:	Standardizing language across protocols; removing double-barrier terminology

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 3.1, 23 December 2016)</th><th>Justification for Change</th></tr>
<tr><td></td><td>• ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~
• Intrauterine device (IUD)~~; 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 subject</td><td>• Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
• Intrauterine device (IUD)
• Vasectomy (partner)
• Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
• Abstinence, if in line with the preferred and usual lifestyle of the subject</td><td></td></tr>
<tr><td>Synopsis, Exclusion Criteria
Section 8.3 Subject Exclusion Criteria</td><td>3. Mean total bilirubin >~~3~~x ULN</td><td>Mean total bilirubin >**5**x ULN</td><td>Rationale 7</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Hepatic encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities already confirmed by biopsy</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td>Rationale 5

Rationale 10</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		Progression to cirrhosis — **Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated**	
Synopsis, Statistical Methods Analysis Populations	The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population.
Synopsis, Statistical Methods, Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints.	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints.	
Synopsis, Statistical Methods, Other Efficacy Analyses Section 13.1.5 Additional	***Insertion***	**Progression to cirrhosis will be assessed in the subset of subjects considered non-cirrhotic at baseline using available medical history, clinical, and laboratory assessments as well as baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be**	Rationale 10

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Secondary Efficacy Analyses		**considered non cirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the trial in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of non-cirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.** **Analyses for the histological assessment conducted as part of the biopsy sub-study are defined in Appendix C.**	
Synopsis, Statistical Methods, Safety Analyses	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will ~~compare OCA and placebo using~~ the Safety Population.	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will **be summarized by treatment group for** the Safety Population.	Clarification of summary analyses
Synopsis, Statistical Methods, Sample Size Justification	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up • ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **subject** accrual and 6 years of follow up • **Two interim analyses and one final analysis are planned** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	Rationale 4 Rationale 3
Section 5.6 Summary of Known Potential Risks with OCA	~~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).~~	**An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg and in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies.**	Language has been updated to reflect Sponsor standards

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	Insertion	**Refer to the IB for additional information regarding the known potential risks with the investigational product.**	
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3). The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5**× ULN or ALP >**3**× ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**….based on tolerability **and biochemical response** (see Section 7.3) The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 1 Rationale 9 Clarification Rationale 7 Rationale 3
Section 7.1.2 Schedule of Study Procedures, Table 1	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration** • **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	[j] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments at Day 0 and Month 12)
	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	[m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds**: unless HCC has already confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis. Rationale 8
	[o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. …	[p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. …	Clarification
	[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a baseline (e.g. Day 0) genetic sample is not obtained, subsequent genetic samples are not**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		required to be collected during the course of the study.	
Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions***	Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis
	[i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~ Not required if done within ~~6~~ months of visit.	[i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. Not required if done within **3** months of visit	
	Insertion (subsequent footnotes are renumbered accordingly)	**[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Not required if done within 6 months of visit.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments)
	[j] Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices.	**[k]** Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices.	
	[k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: **unless HCC has already been confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	are expected to have a minimum follow-up time of approximately 6 years.	are expected to have a minimum follow-up time of approximately 6 years.	
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study.	Rationale 9
Section 7.3 Planned Dosing Regimen	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score ***Footnotes were re-ordered*** [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin >ULN**. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Rationale 8
Section 7.4 Dose Titration Criteria	***Insertion***	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total**	Added language to clarify titrations (up or down)

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.	
Section 8.4.1.1 Severe Drug-Induced Liver Injury	***Insertion***	**If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. Subjects who develop significant drug-induced liver injury which is considered 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, evidence of 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.** **Severe drug induced-liver injury that is not considered related to investigational product must be discussed with the Sponsor before investigational product is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed**	Added guidelines for subjects who develop severe Drug-Induced Liver Injury

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time. **All suspected drug-related hepatic injury events will be adjudicated by the Hepatic Safety Committee (see Section 13.4).**	
Section 8.4.1.2 Liver Transplantation	***Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product***	**8.4.1.2 Liver Transplantation** **Subjects must discontinue investigational product after undergoing liver transplantation surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection.**	The relocation of this statement from within Section 8.4.2 to 8.4.1.2 clarifies directions to discontinue subjects who undergo a liver transplant from investigational product but not study visits
Section 8.4.2 Reasons for Mandatory Interruption of Investigational Product	***Insertion/Reorganization***	**8.4.2 Reasons for Mandatory Interruption of Investigational Product** **Prior to re-starting investigational product after a prolonged interruption, the subject must be re-consented and new baseline visit procedures must be performed if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.**	This clarifies what should be done when a subject experiences a prolonged interruption in investigational product such as in the event of pregnancy
Section 8.4.2.1 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product	**8.4.2.1 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product	Language simplified and aligned with Sponsor standards

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~	**immediately,** but should continue with the study visit schedule. **As described in Section 12.1.9** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.9). New baseline procedures should include pregnancy testing.**	
Section 8.4.3 Other Reasons for Discontinuation of Study of Investigational Product	8.4.2 Other Reasons for Discontinuation of Study of Investigational Product Subjects ~~that~~ discontinue investigational product are expected to continue in the study until the end of the study~~, and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ or at the discretion of the Sponsor.~~ If~~ a subject~~ reaches an event,~~ he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who ~~choose to~~ discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and~~	**8.4.3** Other Reasons for Discontinuation of Study of Investigational Product 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. **With the exception of liver transplant, if** a subject **experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor):	Discontinuation of investigational product language updated to clarify the process that is to be followed after discontinuation and instruct subjects to continue regular visit schedule.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~the study will only terminate~~ (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or cardiovascular events~~. ~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.~~	– 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), liver-related clinical outcomes, and drug-related hepatic injury events.** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** To determine which dosing regimen subjects should follow, the presence or absence of 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~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as non-cirrhotic at baseline per the criteria listed in Section 9.7.3.1 exhibits any of those same criteria (excluding biopsy results consistent with PBC Stage 4), the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites**	Provides detail around the assessment of Progression to Cirrhosis as a secondary endpoint

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		participating in the paired biopsy sub-study (see Appendix C**) must confirm progression to cirrhosis by biopsy. All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	
Section 9.7.6 Screening Procedures	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN).	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5**× ULN and/or an ALP >**3**× ULN).	Reflects new inclusion criteria
Section 9.7.7 Day 0 Procedures	• Perform transient elastography ~~(TE; at selected study sites, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Perform transient elastography **at all study sites with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	Clarifies use of TE and modifies the time during which an historic TE report remains valid
Section 9.7.8 Month 1 Procedures Section 9.7.10 Post-titration visit Procedures	***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:	• **Perform a physical examination.** – In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit **laboratory** requirements:	Physical examinations 1 month after initiating dosing with investigational product will enhance safety monitoring Returning to the site for monthly laboratory assessments can present a significant burden on subjects, thus alternatives are provided for collecting lab samples; with the addition of the physical exam as well the requirement for these exams is provided in the context of the alternatives for laboratory specimen collection

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion***	• **Perform a physical examination** • **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	TE assessment has been added as biannual assessment at all study sites with access to Fibroscan® TE device Hepatic ultrasound should be performed biannually per AASLD and EASL guidelines for subjects with PBC
Section 11.1.2 Secondary Assessments	***Insertion***	• **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.** • **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (see Appendix C)**	Rationale
Section 11.1.2.4 Potential Clinical Outcome Events	The events listed in ~~Appendix A~~ will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	The events listed in **Section 12.1.5** will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	Appendix referencing clinical outcomes events was removed due to redundancy
Section 12.1.4.2 Reporting of Serious Adverse Events	***Insertion***	**Redacted medical record source documentation will be requested for all SAEs and emergency room visits.**	Added sentence regarding redacted medical records to align with Sponsor safety standards
Section 12.1.5 Suspected Liver-Related Clinical Outcome Events	~~For~~ liver-related clinical outcome events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, ~~please refer to Section 11.1.2.4.~~	**Given that the** liver-related 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 liver-related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes**	Updated to align with modified standard safety procedures and Sponsor standard language

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), and spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).	**endpoint. These events will be selected as a "study event" on the Adverse Event CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.** The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).**	
Section 12.1.7 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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours).	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 12.1.4.2.	Updated to align with modified safety procedures and Sponsor standard language
Section 12.1.8 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. Note that longer follow-up can sometimes reveal an off-drug repetition**	Updated to align with modified standard safety procedures and Sponsor standard language

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.	
Section 12.1.9 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~~ investigational product and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing~~ or ~~emailing~~ to ~~the Sponsor at~~ +1 800 497 8521 or sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use of investigational product.~~ The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β-hCG test (see~~ Section 8.4.1~~).~~	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 8.4.2.1) 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** sae@interceptpharma.com **or faxed to** +1 800 497 8521. **The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.** The subject may **re-start** 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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**	Updated to align with modified standard safety procedures and Sponsor standard language

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 3.1, 23 December 2016)</th><th>Justification for Change</th></tr>
<tr><td></td><td></td><td>reporting procedures described in Section 12.1.4 must also be followed.</td><td></td></tr>
<tr><td>Table 10 List of Laboratory Analytes</td><td><table><tr><td>~~Measurement of Liver Fibrosis~~</td><td>~~Fibroscan~~</td></tr><tr><td>~~Bone Density Assessment~~</td><td>~~DEXA~~</td></tr><tr><td>Other</td><td>Insertion</td></tr></table></td><td>Deletion<table><tr><td>Other</td><td>OCA-glucuronide</td></tr></table></td><td>Measurements of liver fibrosis are captured in a different section

OCA-glucuronide was listed in the text but missing from the table</td></tr>
<tr><td>Section 13.1.1 Analysis Populations</td><td>~~• The Randomized Population will include all randomized subjects~~</td><td>Deletion</td><td></td></tr>
<tr><td>Section 13.1.2.1 Sample Size Monitoring</td><td>9.1.2.1 Sample Size ~~Re-Estimation Plan~~
~~Therefore, starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups.
~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative~~</td><td>9.1.2.1 Sample Size Monitoring
Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups.
Deletion</td><td></td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~primary efficacy analysis is specified is Section 13.1.9.~~ ~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~		
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between the effect of OCA on ALP and bilirubin and the clinical benefit of OCA will be evaluated by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This analysis will be based on the ITT population.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
13.1.8 Supportive Analysis	***Insertion***	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1), using**	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		similar statistical methodology as specified above. **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	Sponsor has received agreement from regulatory authorities.
Section 13.1.9 Alternative Primary Analysis	~~13.1.9 Alternative Primary Analysis~~ ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section **13.1.2.1**). Similar statistical methodology as specified above in Section **13.1.8** for supportive analyses will be utilized.~~ ~~The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section **13.1.8** will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~	***Deletion***	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the Sponsor has received agreement from regulatory authorities

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs and/or loss of patients to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy or futility) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.**	Explanation of the type of review that will be ongoing by the DMC during study conduct.
Section 19 List of References	***Insertion***	**Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential**	Additional relevant references were added.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.	
Appendix B List of Study 747-302 Outcome Events	~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~	**Deleted**	Redundant; Information is contained within the protocol
Appendix C Biopsy Sub-Study of Protocol 747.302: A Phase 4, Double-Blind, Randomized, Placebo-Controlled,	***Insertion***	**See Appendix C**	The purpose of this sub-study is to assess the effect of OCA versus placebo on the histological severity of disease (fibrosis/cirrhosis) in subjects with PBC. In addition, this sub-study will demonstrate the relationship between

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in subjects with Primary Biliary Cholangitis			histological changes and clinical, laboratory, and non-invasive measures indicative of progression to cirrhosis in patients with PBC.

APPENDIX H. SUMMARY OF CHANGES: PROTOCOL VERSION 3.1 TO PROTOCOL VERSION 4 (DATED 10 MAY 2017)

Please note that Protocol 747-302 Version 3.1 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. A full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided in Appendix I.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 Version 3.1 include:

- Hepatocellular carcinoma (HCC) has been redefined as a secondary endpoint;
- Following the broadening of the spectrum of disease, a commitment to enroll a minimum of 30% of subjects with abnormal bilirubin has been added to the protocol;
- Clarifications have been incorporated throughout the protocol based on the addition of a biopsy substudy in Addendum 2;
- Statistical language has been modified and added to clarify statistical assumptions and analyses including the addition of a Per Protocol (PP) Population;
- Background rationale has been updated to reflect the current approval status of Ocaliva; and
- Safety language has been updated throughout the protocol to reflect the updating of Sponsor standards.

Minor revisions include editorial changes such as removal of hyphens and capitalization of words. Minor revisions may be included in the following table when they are also part of major revisions; however, most minor/editorial changes and nonsubstantial changes are not listed individually.

The text deleted from Protocol Version 3.1 is crossed out while revised text in Version 4 is indicated in bold font in the table below.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Study Personnel Contact Information	~~**Or if Not Available:**~~ ~~Contact:~~ PPD ~~MD, PhD Medical Director, Clinical Research,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~Mobile:~~ PPD ~~(Pacific time zone)~~ ~~Email:~~ PPD PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD PPD ~~Clinical Operations,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~(Pacific time zone)~~ ~~Mobile:~~ PPD ~~Fax:~~ PPD ~~Email:~~ PPD		Updating emergency medical monitor contact information. The contact information for clinical operations and project management personnel is no longer required in the protocol per Sponsor's procedures.
Synopsis, Objectives, Primary, Statistical Methods – Efficacy Analyses	To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary ~~cirrhosis~~ (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:	To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary **cholangitis** (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:	Editorial correction HCC has been redefined as a secondary endpoint instead of a component of the primary

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy~~		composite-event endpoint per Regulatory Authority request.
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***In Section 6.2*** To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above ~~and also to include liver related death~~. To ~~characterize~~ the effect of OCA compared to placebo on progression to cirrhosis. To ~~assess~~ the PK of OCA and its conjugates in a subset of subjects.	**To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).** To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above. **To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.** To **assess** the effect of OCA compared to placebo on progression to cirrhosis. To **characterize** the PK of OCA and its conjugates in a subset of subjects.	HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request. Editorial change Editorial change Editorial change
Synopsis, Methodology Section 7.1, Overall Study Design.		**A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.**	To ensure enrollment of an adequate number of subjects with abnormal total bilirubin.

<table>
<tr><th>Section</th><th>Original Text
(Amendment 3.1, 21 December 2016)</th><th>Revised Text
(Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td>Section 7.1.1
Study Design Diagram,
Fig 1 (Footnote)</td><td>Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response.</td><td>Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN).</td><td>Clarification of biochemical response</td></tr>
<tr><td>Synopsis, Number of Subjects (Planned)

Section 7.2
Number of Subjects</td><td>Insertion in both, Synopsis and Section 7.2

Change in Synopsis section

Approximately 428 subjects</td><td>In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

Approximately 428 subjects are planned to be enrolled in the study.</td><td>Language added to allow for continued enrollment into the biopsy substudy; additional subjects are not anticipated to prolong the duration of the study.</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td></td><td>• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy.~~</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td></td><td></td></tr><tr><td>Secondary Objectives</td><td></td></tr><tr><td>HCC</td><td>Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy</td></tr></table></td><td>HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.</td></tr>
<tr><td>Synopsis, Statistical Methods
Analysis Populations</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBC Historical Control.</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP), Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBC Historical Control.</td><td>The randomized population is included within the Safety population.
The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.</td></tr>
</table>

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Primary Efficacy Endpoint Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	~~• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~ ***Section 13.1.3*** ~~• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy~~ The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	***Section 13.1.3*** The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request. Editorial change
Synopsis, Statistical Methods, Primary Efficacy Analysis Section 13.1.3 Primary Efficacy Analysis	***Insertion***	**The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses Section 13.1.4 Secondary Efficacy Analysis	***Insertion*** ***Section 13.1.4*** The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in the ITT population with respect to the key secondary efficacy endpoints.	**The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.** ***Section 13.1.4*** The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints.	The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints. Editorial change

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Additional Secondary Efficacy Analyses	~~Other~~ Efficacy Analyses The following secondary efficacy analyses will compare OCA ~~to~~ placebo ~~on time to the following events~~: • Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above) • Development of varix/varices • Liver-related death • Liver-related death or liver transplant Liver-related death, liver transplant, or MELD score ≥15	**Additional Secondary** Efficacy Analyses The following **time-to-event** secondary efficacy analyses will compare OCA versus placebo using **the ITT population**: • **Time to e**ach component of the primary efficacy endpoint (except MELD score ≥15 which is listed above) • **Time to d**evelopment of varix/varices • **Progression to cirrhosis** • **Time to occurrence of HCC** • **Time to l**iver-related death • **Time to l**iver-related death or liver transplant **Time to l**iver-related death or liver transplant, or MELD score ≥15	Editorial Change Progression to cirrhosis added as secondary endpoint in Version 3.1. HCC has been redefined as a secondary endpoint instead of a component of the primary composite event endpoint per Regulatory Authority request.
Synopsis, Statistical Methods, Additional Secondary Efficacy Analyses Section 13.1.5 Additional Secondary Efficacy Analyses	***Insertion*** Analyses for the histological assessment conducted as part of the biopsy substudy are defined in ~~Appendix C~~.	**For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy.** Analyses for the histological assessment conducted as part of the biopsy substudy are defined in **Addendum 2.**	Provides further details of progression to cirrhosis as outlined in the biopsy substudy defined in Addendum 2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	***Insertion*** The following assumptions were used in sample size calculations: • Two interim analyses and one final analysis are planned. ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to ~~clinical~~ outcomes.	**The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN.** The following assumptions were used in sample size calculations: • Two interim analyses and one final analysis are planned. **The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.** • **A dropout rate of 10% is assumed.** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to **liver-related** outcomes**, including all-cause mortality**.	Incorporation of the broadened spectrum of disease into the sample size justification. Clarification of interim analyses. Clarification of the assumed dropout rate. Clarification of outcomes being assessed in power calculations.
Section 5.1 Overview of PBC and OCA	5.1. Overview of Primary Biliary ~~Cirrhosis~~ and Obeticholic Acid Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis~~)~~ 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	5.1. Overview of Primary Biliary **Cholangitis** and Obeticholic Acid 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	Updating language to include accelerated and conditional approvals of OCA in the US and EU.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	necessitates liver transplantation or results in death. Ursodeoxycholic acid (UDCA), a physiological constituent of human ~~bile , is currently the only treatment approved for PBC~~ (Lindor 2009). While UDCA therapy ~~has~~ a marked effect on the treatment of PBC, up to 50% of patients ~~show~~ a suboptimal response or no response to UDCA. Such patients ~~are~~ at significantly increased risk of a poor clinical outcome due to PBC disease progression~~. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]).~~ Obeticholic acid (OCA) ~~is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.~~ ~~OCA is a modified bile acid and~~ farnesoid X receptor (FXR) agonist ~~that is~~ derived from the primary human bile acid chenodeoxycholic acid (CDCA~~). OCA is currently being developed in the United States (US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States~~ Food and Drug Administration	necessitates liver transplantation or results in death. **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**), 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 (Pellicciari 2002). 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.	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	(FDA) ~~has~~ granted accelerated approval for Ocaliva ~~for the treatment of PBC.~~ Ocaliva ~~is not yet approved outside the United States for use in any~~ indication.		
Section 5.4 Overview of PBC and OCA	As of 31 Jan ~~2016~~, approximately ~~1726~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ subjects had PBC, ~~330~~ subjects had NASH, 41 subjects had diabetes mellitus/~~non-alcoholic~~ fatty liver disease ~~(NAFLD)~~, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~20~~ subjects had primary sclerosing cholangitis (~~PSC~~).	As of 31 Jan **2017**, approximately **2186** subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** subjects had PBC, **686** subjects had NASH, 41 subjects had diabetes mellitus/**nonalcoholic** fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **52** subjects had primary sclerosing cholangitis, **and 5 subjects had biliary atresia.** **----------** **[1]Includes estimated numbers from ongoing blinded studies.**	Language updated to include data from current IB.
Section 5.5.2.1 Rationale for OCA Dose	The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; ***Insertion*** Based on these data, ~~the indicated commercial doses of~~ OCA for the treatment of patients with PBC are 5 mg and 10 mg. ~~As such,~~ Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.	The Phase 3 PBC study **(Study 747-301)** subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; **Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus.** Based on these data, the **approved dosing regimens for** OCA for the treatment of patients with PBC are 5 mg and 10 mg. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose **for at least 3 months**, increasing to 10 mg OCA, if tolerated.	Provides rationale for the dosing in alignment with commercial labeling.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 5.6 Summary of Known Potential Risks with OCA	~~An increase in liver enzymes and~~ hepatic ~~AEs, including jaundice,~~ were observed in ~~subjects with liver disease at OCA doses between 10 mg and 50 mg and in~~ healthy ~~subjects who were~~ treated ~~at doses ≥100 mg in Phase 1,~~ multiple-~~dose studies~~. These findings were seen more frequently with doses ~~above~~ 10 mg OCA.	**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)**. 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).**	Language has been updated to reflect Sponsor standards.
Section 7.1.2 Schedule of Study Procedures, Table 1	[a] All subjects will have the chemistry panel retested to ensure subjects have two ALP and bilirubin assessments 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. [l] Endoscopy will be conducted at ~~selected~~ study sites where the device is available. [m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met~~.	[a] All subjects will have the chemistry panel retested to ensure subjects have **at least** two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. **Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility.** [l] Endoscopy will be conducted at **all** study sites where the device is available**.** [m] 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**.	Editorial changes
Section 7.1.2 Schedule of Study Procedures, Table 2	[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. ~~Not required if done within 3 months of visit.~~	[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available.	Editorial changes

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. ~~Not required if done within 6 months of visit~~. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met.~~	[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, postday 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm **suspected HCC**.	
Section 7.4 Dose Titration Criteria	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.	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, **biochemical response**, and clinical judgment. **Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).**	Editorial changes
Section 7.4.1 Pre-Titration Tolerability Assessment Requirements	• There must be no clinically significant increase (as determined by the ~~i~~nvestigator) in the subject's liver function tests. ~~Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19 should be implemented, as required.~~	• There must be no clinically significant increase (as determined by the **I**nvestigator) in the subject's liver function tests.	Clarification
Section 7.4.2	***The text in this section is moved to Section 8.4.***		To avoid redundancy

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Safety Criteria for Adjustment or Stopping Doses			
Section 8.4 Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	**[*Moved from Section 7.4.2 of Version 3*]** Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be **adjusted back** to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved. Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an **outcome** event, he or she should continue the regular visit schedule and continue taking investigational product as long as the **subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the** Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Clarification
Section 8.4.1.1 Reasons for Additional Monitoring Related to Liver Chemistries	***Modification of 8.4.3.1 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~~	**Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total**	Clarified guidelines for subjects who develop elevations in liver chemistries. Language related to interruption of investigational product is now located in Section 8.4.1.2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~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.~~	**bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored.**	
Section 8.4.1.2 Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	***Insertion***	**Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3x baseline (and >ULN)** • **Total bilirubin >2x 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 AE information should also be collected and the subject 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**	Clarified guidelines for subjects who develop elevations in liver chemistries.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		medications should be identified and discontinued if advisable. **If symptoms persist or repeat testing shows AST or ALT >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 investigative product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject 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**	

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		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 subject 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.** Subjects who develop **evidence of severe** drug-induced liver injury, which 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. **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 subjects 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**	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Section 8.4.1.1: Subjects who develop ~~significant~~ drug-induced liver injury which is ~~considered~~ 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, ~~evidence of~~ functional hepatic impairment as indicated by rising bilirubin or INR that cannot be explained by progression of disease. ***Insertion***	**appropriate for the subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.** **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 13.4).**	
Section 8.4.1.3 Pregnancy	**8.4.2.1 Pregnancy** As described in Section ~~12.1.9~~ pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 ~~12.1.9~~). ~~New baseline procedures should include pregnancy testing~~.	**8.4.1.3 Pregnancy** As described in Section **12.1.11** pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 **12.1.11**.	Revised section number.
Section 8.4.2.1 Liver Transplantation	**8.4.1.2 Liver Transplantation** Subjects must discontinue investigational product ~~after undergoing liver transplantation surgery.~~ Subjects should be encouraged to ~~continue study visits, despite stopping investigational product, for continued study data collection~~.	**8.4.2.1 Liver Transplantation** Subjects **who undergo a liver transplant during the course of the study** must discontinue investigational product **and discontinue the study visit schedule. However, these** subjects 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**.	Clarification on process for subjects who undergo a liver transplant.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 8.4.3 Other Reasons for Discontinuation of Study or Investigational Product	~~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. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18).~~ – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess suspected major adverse cardiovascular events (MAC), liver-related clinical outcomes~~, and drug-related hepatic injury events~~.	– Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess suspected major adverse cardiovascular events (MACE) **and** liver-related clinical outcomes. – **Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.18).**	Clarification of process
Section 9.7.1 Visit Windows	Screening |	Screening | **See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.**	
Section 9.7.3.2 Progression to Cirrhosis	When a subject identified as ~~non-cirrhotic~~ at Baseline per the criteria listed in Section 9.7.3.1 exhibits any ~~of those~~ same criteria ~~(excluding biopsy results consistent with PBC Stage 4)~~, the	When a subject identified as **noncirrhotic** at Baseline per the criteria listed in Section 9.7.3.1 exhibits any **signs or symptoms associated with progression to cirrhosis, as defined by the** same	Details the assessment of progression to cirrhosis.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites participating in the paired biopsy ~~sub-study (see Appendix C)~~ must confirm progression to cirrhosis by biopsy.	criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy **(centrally read)** unless not medically indicated. **Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis.** **Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.** Sites participating in the paired biopsy **substudy** must confirm progression to cirrhosis by biopsy **as per the information outlined in protocol Addendum 2.**	
Section 9.7.6 Screening Procedures	~~Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated~~ serum chemistry samples (at least 2 weeks apart) ~~to confirm~~ pretreatment ALP and total bilirubin ~~values~~: ***Insertion***	**Collection of 2 s**erum chemistry samples (**collected** at least 2 weeks apart**) during Screening is required for confirmation of the** pretreatment **serum chemistry values, including the** ALP and total bilirubin **used to determine eligibility**: • **When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Allows repeat assessments when baseline laboratory values are discrepant between Screening Visit 1 and Screening Visit 2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	• …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (~~selected~~ study sites ~~only~~), ***Insertion***	• …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 **(at all** study sites **where the device is available**), **In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.**	
Section 9.7.8 Month 1 Procedures Section 9.7.10 1-Month Post-Titration visit Procedures	***Insertion (9.7.8)*** ***Insertion (9.7.10)***	– **A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed**. – **A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed**.	Clarification
Section 9.7.12 Month 9 Procedures Section 9.7.14 Month 12 Procedures Section 9.7.16 Month 16 Continued Follow-Up Procedures Section 9.7.17 Month 12 Follow-up Procedures Section 9.7.18 EOS/EOT	***Section 9.7.12, 9.7.14, 9.7.16, 9.7.17, and 9.7.18*** *…DEXA procedure to be done at* ~~selected~~ study sites ~~only~~, ***Section 9.7.14, and 9.7.17*** • Perform an endoscopy (at ~~selected~~ study sites, where available)	***Section 9.7.12, 9.7.14, 9.7.16, 9.7.17, and 9.7.18*** *…DEXA procedure to be done at* **all** study sites **where the device is available** ***Section 9.7.14, and 9.7.17*** • *Perform an endoscopy (at **all** study sites, where **device is** available)*	Clarification

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 9.7.18 EOS/EOT	If the subject reports having eaten within 8 hours, document accordingly in the source and CRF ~~and remind the subject that fasting is required prior to all study visits~~.	If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.	Clarification
Section 10.3 Investigational Product Storage	~~The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical study 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.**	Updating temperature excursions language per Sponsor stability studies.
Section 11.1.2 Secondary Assessments	***Insertion*** • Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in ~~Appendix C~~). • Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c reactive protein (CRP), tumor necrosis factor α (TNF-α), FGF 19, cytokeratin-18 (CK-18) and ELF, (and others as determined during the course of the study).	• **Individual components of the primary endpoint.** • Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in **Addendum 2**). • **HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.** • Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c reactive protein (CRP), tumor necrosis factor α (TNF-α), FGF 19, cytokeratin-18 (CK-18) ELF, and **Fibroscan** (and others as determined during the course of the study). • **Clinical outcomes, including individual component of the primary endpoint**	Clarified and re-ordered bullets for consistency throughout document. Addition of Addendum 2. Reflects addition of a biopsy substudy available to interested sites in Addendum 2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		(where available), liver transplant, and death will be compared to historical controls. • **PK of OCA and its conjugates.** • Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.	
	• Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.		
Section 12.1.3 Relationship of Adverse Events to Liver Biopsy	***Insertion (new section)***	**The Investigator will document her/his opinion of relationship of an AE to liver biopsy using the criteria outlined in Table 9.** **Table 9: Relationship of Adverse Events to Liver Biopsy** **Relationship** / **Description** **Related** — **A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.** **Not Related** — **Any event that does not meet the above criteria.**	Added with the addition of liver biopsies for the confirmation of progression to cirrhosis.
Section 12.1.5.2 Reporting of Serious Adverse Events	~~•Telephone: +1 858 964 1571~~ 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.	If an SAE is reported by **email** or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible.	Updated to align with modified standard safety procedures.
Section 12.1.6 Suspected Liver-Related Clinical Outcome Events	***Section 12.1.5*** Given that the liver-related 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 liver-related clinical outcome events in order to retain the study	***Section 12.1.6*** Given that the liver-related clinical outcome events **may** also meet the criteria of a SUSAR, **but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly,** the Sponsor will not expeditiously report suspected	Updated to align with modified standard safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	blind and preserve the integrity of the clinical outcomes endpoint. The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).	liver related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 **or oesophageal varices haemorrhage**), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological **or clinical** progression to cirrhosis (preferred term: hepatic cirrhosis).	
Section 12.1.8 Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	***Insertion (new section)***	**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 12.1.5.2.** **SAEs that occur in subjects 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 12.1.5.2.**	Updated to align with modified safety procedures and Sponsor standard language.
Section 12.1.9 Notification of Poststudy SAEs	***Section 12.1.7*** All SAEs that occur within 30 days following the ~~cessation of investigational product~~, whether or	***Section 12.1.9*** All SAEs that occur within 30 days following **discontinuation from the study,** whether or not	Updated to align with modified safety procedures

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.~~4.~~2. ~~SAEs that occur more than 30 days after a subject has discontinued investigative product, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with investigative product, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.~~	they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.**5**.2.	and Sponsor standard language.
Section 12.2.7 Laboratory Assessments	The list of laboratory analytes to be tested is shown in Table 1~~0~~.	The list of laboratory analytes to be tested is shown in Table 1**1**, **and the normal reference ranges for liver biochemistries are shown in Appendix C.**	Added per Regulatory Authority request.
Section 13 Statistical Methods	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to ~~study database lock~~, propensity score determination, and unblinding of the double-blind subject treatment assignments.	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the **first interim analysis**, propensity score determination, and unblinding of the double-blind subject treatment assignments.	Reflects addition of interim analyses to the study protocol.
Section 13.1.1 Analysis Populations	***Insertion***	• **The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.**	The Per Protocol Population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.1.1 Comparability of Historical Controls	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria ~~where possible~~.	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. **Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8**.	Clarifies the use of propensity scores in the assessment of the historical control population.
Section 13.1.5 Additional Secondary Efficacy Analyses	The following secondary efficacy analyses will compare ~~randomized~~ OCA ~~to randomized~~ placebo on using the ITT population:	The following **time-to-event** secondary efficacy analyses will compare OCA versus placebo using the ITT population: • **Progression to cirrhosis** • **Time to occurrence of HCC**	Editorial Change Progression to cirrhosis added as secondary endpoint in Version 3.1. HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	The association between ~~the effect of OCA on~~ ALP and bilirubin and the clinical benefit of OCA will be evaluated ~~by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This~~ analysis will be ~~based on~~ the ~~ITT population~~. Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.	The association between **biochemistry including** ALP and bilirubin **with clinical outcomes will be assessed** and the clinical benefit of OCA **using biochemistry as a surrogate endpoint** will be evaluated. **Detailed** analysis will be **described in** the **SAP**. Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of **OCA using biochemistry as a surrogate endpoint** for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.8 Supportive Analysis	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment. ~~Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a~~ full range of covariates across which the treatment and historical controls might differ. Only covariates and not outcome variables will be included in the propensity score estimation. ~~Therefore, there is no chance of biasing,~~ to avoid biased results that are in favor of one treatment.	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, **which serves as an external control for supportive analysis**. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment **between the treated subjects and the matched natural history subjects**. **A** full range of covariates across which the treatment and historical controls might differ **will be considered to mitigate potential bias**. Only covariates and not outcome variables will be included in the propensity score estimation **to avoid biased** results **that are** in favor of one treatment. **The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.** **A third-party statistician(s) will perform the propensity score modeling and matching. This**	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis. Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses. The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	
	The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes: • ~~Time to hepatocellular carcinoma~~		
Section 13.1.9 Handling of Dropouts or Missing Data	***Insertion***	**In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.**	Clarification of statistical analyses to address missing data.
Section 13.1.11 Examination of Subgroups	The primary and secondary efficacy endpoints will be analyzed for subject subgroups ~~(eg, age, sex, and race)~~ based on the ITT population. ***Insertion***	The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. **The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)** • **Early (normal albumin and normal bilirubin)**	Added per Regulatory Authority request.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Moderate (abnormal albumin or abnormal bilirubin)** • **Advanced (abnormal albumin and abnormal bilirubin)** **The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.** • **Monotherapy in patients who are intolerant or non-responsive to UDCA** • **Elderly patients** **Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.** **Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
Section 13.1.12 Continuous Monitoring and Interim Analyses	Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively. The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy ~~or futility~~) of the study beyond each interim analysis.	Both interim analyses will be pre-specified and will occur after accrual of 50% **(64 events)** and 75% **(96 events)** of clinical outcome events, respectively. The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation,	Added number of anticipated events. Clarification

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		modification, or cessation (for efficacy) of the study beyond each interim analysis	
Section 19 List of References	~~Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.~~ ***Insertion***	**Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Digestive and Liver Disease. 2015a;47(11):924-6.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6α-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-3572.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	Additional relevant references were added.
Appendix C Reference Laboratory Values from Central Laboratories	***Insertion (new appendix)*** ***Deletion:*** ***Appendix C in Version 3.1 has been deleted. It is now published as Protocol Addendum 2.***	***Appendix containing reference laboratory values from central laboratories added.***	Added per Regulatory Authority request.

APPENDIX I. SUMMARY OF CHANGES: PROTOCOL VERSION 3 TO PROTOCOL VERSION 4 (DATED 10 MAY 2017)

Please note that Protocol 747-302 Version 3.1 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. Therefore, a full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided below.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the modification of inclusion/exclusion criteria to expand the PBC disease spectrum, the addition of progression to cirrhosis as a secondary endpoint, and the addition of 2 interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

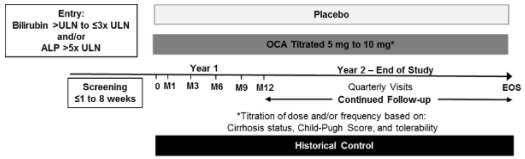
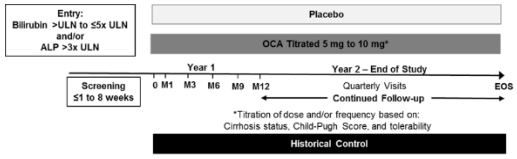
The text deleted from Protocol Version 3 is crossed out while revised text in Version 4 is indicated in bold font. Minor/editorial changes and non-substantial changes are not listed individually. For efficiency, rationales that impact multiple sections are provided below and referenced in the table with the corresponding rationale number.

1. **The phase of the study has been changed from "3b" to "4"** to reflect that this is a post-marketing study. Protocol 747-302 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC, ie, in the US and the EU. In all other regions, this study is considered Phase 3b. In May 2016, the FDA granted accelerated approval for OCA (Ocaliva) for the treatment of PBC. In December 2016, Ocaliva received Conditional Approval from the European Medicines Agency's Committee for Medicinal Products for Human Use.
2. **The term "primary biliary cirrhosis"** has been changed to "primary biliary cholangitis" to reflect recent changes in the nomenclature for PBC.
3. **The number of required adjudicated events for the final analysis has increased** from 121 to 127 due to the addition of two interim analyses, which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy) of the study. One interim analysis will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). In addition, inclusion of PBC subjects with earlier stage disease will increase the time to event, thereby requiring more events to maintain follow-up to approximately 6 years.
4. The first-year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by 2 years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.

5. "**Encephalopathy"** has been modified to "Hepatic Encephalopathy" to clarify that the relevant Clinical Outcome Event should be related to hepatic disease.
6. **Hepatocellular carcinoma** (HCC) has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.
7. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of HCC.
8. **Broadening the Spectrum of Disease**: Lowering the minimum allowable baseline ALP from >5x ULN to >3x ULN and raising the maximum allowable baseline total bilirubin to ≤5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the Phase 3 protocol 747-301. However, to ensure enrollment of an adequate number of subjects with abnormal total bilirubin, a minimum of 30% of the subjects enrolled in the study will have elevated bilirubin (>ULN) at Screening.
9. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
10. The increase in enrollment from 350 to 428 subjects is due in part to the increased number of events from two additional interim analyses, and in part due to the change in the estimated placebo baseline hazard rate, which resulted from changing the lower limit of ALP from >5x ULN to >3x ULN in the enrollment criteria #2.
11. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential noninvasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of Study 747-302.
12. **A Per Protocol (PP) population** has been added to the statistical analysis section. Sensitivity analysis for primary efficacy endpoints and key secondary efficacy endpoints will be performed using PP population.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD PPD ~~Clinical Operations,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~(Pacific time zone)~~ ~~Mobile:~~ ~~Fax:~~ PPD	**O**	The contact information of clinical operations and project managements personnel is no longer required per Sponsor's procedures.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Email:~~ PPD PPD		
Synopsis, Studied Period (Years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	Phase ~~3b~~	Phase **4**	Rationale 1
Synopsis, Objectives, Primary, Statistical Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• Encephalopathy (as defined by a West Haven score of ≥2) • ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5 Rationale 6
Synopsis, Objectives, Secondary	To assess the effect of OCA compared to placebo on time to first occurrence of each individual	To assess the effect of OCA compared to placebo on time to first occurrence of each individual	Rephrasing the objective

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 6.2 Secondary Objectives	component of the primary endpoint as listed above ~~and also~~ to include liver related death. ***Insertion*** To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects	component of the primary endpoint as listed above. **To assess the effect of OCA compared to placebo on time to occurrence of** liver-related death. **To assess the effect of OCA compared to placebo on progression to cirrhosis.** **To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).** To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 11 Rationale 6
Synopsis, Methodology: Schematic Diagram Section 7.1.1 Study Design Diagram, Figure 1	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching	**A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.**  Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN)**. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study	Rationale 8 Rationale 8 Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. • Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	visit following the Month 3 visit based on tolerability **and biochemical response** of the product. • Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (Planned) Section 7.2 Number of Subjects	***Insertion*** ***Change in Synopsis section*** Approximately ~~350~~ subjects	**In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the sub study may be added to the target subject enrollment number currently planned**. Approximately **428** subjects **are planned to be enrolled in the study.**	Rationale 10 and Addendum 2

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Change in Section 7.2 section It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study to achieve **127** adjudicated primary endpoint events.	
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ≤~~3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 8
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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: • ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~ • Intrauterine device (IUD)~~; 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 subject	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below: • **Barrier** method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide • Intrauterine device (IUD) • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) • Abstinence, if in line with the preferred and usual lifestyle of the subject	Standardizing language across protocols; removing double-barrier terminology.

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td>Synopsis, Exclusion Criteria

Section 8.3 Subject Exclusion Criteria</td><td>2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

3. Mean total bilirubin >~~3~~x ULN</td><td>2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

•History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria

3. Mean total bilirubin >5x ULN</td><td>This criterion (sub-bullet) is already included in Version 3 of the protocol. In the Version 4, it is added to the synopsis for consistency.

Rationale 8</td></tr>
<tr><td>Synopsis, Duration of Treatment</td><td>It is ~~estimated~~ that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue ~~121~~ total primary endpoint events.</td><td>It is expected that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 127 total primary endpoint events.</td><td>Rationale 3</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td>
<table>
<tr><th>Primary Objectives</th><th>Assessments</th></tr>
<tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)

• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~</td></tr>
<tr><td>Secondary Objectives</td><td></td></tr>
</table>
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<table>
<tr><th>Primary Objectives</th><th>Assessments</th></tr>
<tr><td>Clinical outcomes</td><td>– Hepatic encephalopathy (as defined by a West Haven score of ≥2)</td></tr>
<tr><td>Secondary Objectives</td><td></td></tr>
<tr><td>Progression to cirrhosis</td><td>Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated</td></tr>
</table>
</td><td>Rationale 5

Rationale 11

Rationale 6</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		Hepatocellular carcinoma | **Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy**	
Synopsis, Statistical Methods Analysis Populations	The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), **Per Protocol (PP)** Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population. Rationale 12 (for PP Population)
Synopsis, Statistical Methods, Primary Efficacy Endpoint Section 11.1.1 Primary Assessments	The primary efficacy endpoint will be the time to first occurrence of one of the following ~~post randomization~~: • Encephalopathy (as defined by a West Haven score of ≥2) • ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~ ***Change in Synopsis section*** ~~Every event for enrolled subjects~~ will be adjudicated by an independent committee.	The primary efficacy endpoint will be the time to first occurrence of one of the following: • **Hepatic** encephalopathy (as defined by a West Haven score of ≥2) **All events** will be adjudicated by an independent committee.	Rationale 5
Synopsis, Statistical Methods, Primary Efficacy Analysis Section 13.1.3 Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population. ***Insertion***	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. **The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	Rationale 12

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses Section 13.1.4 Secondary Efficacy Analysis	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints. ***Insertion***	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints. **The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	Rationale 12
Synopsis, Statistical Methods, Additional Efficacy Analyses Section 13.1.5 Additional Secondary Efficacy Analyses	~~Other~~ Efficacy Analyses The following secondary efficacy analyses will compare OCA to placebo ~~on time to the following events~~: ***Insertion***	**Additional** Efficacy Analyses The following **time-to-event** secondary efficacy analyses will compare OCA to placebo **using the ITT population**: • **Progression to cirrhosis** • **Time to occurrence of HCC** **Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as Baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for**	Rationale 6 and Rationale 11 Rationale 11

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. **For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2.**	
Synopsis, Statistical Methods, Safety Analyses	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will ~~compare OCA and placebo using~~ the Safety Population.	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will **be summarized by treatment group for** the Safety Population.	Clarification of summary analyses.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to ~~clinical outcomes~~. In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	**The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN.** The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **of subject** accrual and 6 years of follow up. • **Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.** • **A dropout rate of 10% is assumed** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to **liver-related outcomes, including all-cause mortality**. In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	Rationale 8 Rationale 4 Rationale 3
Section 5.1 Overview of PBC and OCA	5.1. Overview of Primary Biliary ~~Cirrhosis~~ and Obeticholic Acid	5.1. Overview of Primary Biliary **Cholangitis** and Obeticholic Acid	Updating language to include accelerated and conditional

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis) 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. ursodeoxycholic acid (UDCA), a physiological constituent of human bile, ~~is currently the only treatment approved for PBC~~ (Lindor 2009). While UDCA therapy ~~has~~ a marked effect on the treatment of PBC, up to 50% of patients ~~show~~ a suboptimal response or no response to UDCA. Such patients ~~are~~ at significantly increased risk of a poor clinical outcome due to PBC disease progression. ~~There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]).~~ Obeticholic acid (OCA)~~ is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.~~ ~~OCA is a modified bile acid and~~ farnesoid X receptor (FXR) agonist ~~that is~~ derived from the primary human bile acid chenodeoxycholic acid (CDCA)~~. OCA is currently being developed in the United States (~~US~~) and Europe for the treatment of PBC and other chronic liver diseases. OCA has~~	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. **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), **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 (Pellicciari 2002). 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**	approvals of OCA in the US and EU.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States~~ Food and Drug Administration (FDA) ~~has~~ granted accelerated approval for Ocaliva ~~for the treatment of PBC.~~ Ocaliva ~~is not yet approved outside the United States for use in any~~ indication.	**UDCA. In December 2016, the European Commission granted conditional approval for** Ocaliva **for the same** indication.	
Section 5.4 Overview of PBC and OCA	As of 31 Jan ~~2016~~, approximately ~~1726~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ subjects had PBC, ~~330~~ subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease ~~(NAFLD)~~, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~20~~ subjects had primary sclerosing cholangitis (~~PSC~~).	As of 31 Jan **2017**, approximately **2186** subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** subjects had PBC, **686** subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **52** subjects had primary sclerosing cholangitis, **and 5 subjects had biliary atresia.** **----------** **[1]Includes estimated numbers from ongoing blinded studies.**	Language updated to include data from current IB.
Section 5.5.2.1 Rationale for OCA Dose	The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; ***Insertion***	The Phase 3 PBC study **(Study 747-301)** subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; **Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus.**	Provides rationale for the dosing in alignment with commercial labeling.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Based on these data, ~~the indicated commercial doses of~~ OCA for the treatment of patients with PBC are 5 mg and 10 mg. ~~As such,~~ Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.	Based on these data, the **approved dosing regimen for** OCA for the treatment of patients with PBC are 5 mg and 10 mg. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose **for at least 3 months**, increasing to 10 mg OCA, if tolerated.	
Section 5.6 Summary of Known Potential Risks with OCA	These findings were seen more frequently with doses ~~above~~ 10 mg OCA. ***Insertion***	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).** **Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.**	Language has been updated to reflect Sponsor standards.
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3).	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5x** ULN and/or ALP >**3**x ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). . . **A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.** **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**…based	Rationale 1 and Rationale 8 Rationale 10 Rationale 8 Clarification Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		on tolerability **and biochemical response** (see Section 7.3)	
	The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 3
Section 7.1.2 Schedule of Study Procedures, Table 1	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration** • **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.
	[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility.	[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. **Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility.**	
	[j] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments at Day 0 and Month 12).
	[k] Endoscopy will be conducted at ~~selected~~ study sites where the device is available.	[m] Endoscopy will be conducted at **all** study sites where the device is available**.**	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met~~.	[m] 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**.	
	[o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. …	[p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. …	Rationale 9
	[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a Baseline (eg, Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.**	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions***	Physical exams have been added at **1-Month Post Titration** Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.
	[i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Not required if done within 6 months of visit.~~ ***Insertion*** (subsequent footnotes are renumbered accordingly)	[i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. [j] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available.**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis. DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments).
	~~[j]~~ Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices.	[k] Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices.	
	[k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met.~~	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. 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**. [o] … The initial dose titration of investigational products may occur at the Month 3 visit, or any	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[e] … The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability.	study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response.**	Rationale 9
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study to achieve **127** adjudicated primary endpoint events. **In the event additional subjects are needed to complete enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned**.	Rationale 10 Language added to allow for continued enrollment into the biopsy substudy; additional subjects are not anticipated to prolong the duration of the study.
Section 7.3 Planned Dosing Regimen, and Table 3	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. ***Footnotes of Table 3 were re-ordered*** [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin are >ULN**. [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 7.4 Dose Titration Criteria	***Insertion*** 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.	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.** 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, **biochemical response**, and clinical judgment. **Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).**	Added language to clarify titrations (up or down).
Section 7.4.1 Pre-Titration Tolerability	• There must be no clinically significant increase (as determined by the ~~i~~nvestigator) in the subject's liver function tests. ~~Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be~~	• There must be no clinically significant increase (as determined by the **I**nvestigator) in the subject's liver function tests.	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Assessment Requirements	~~up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19 should be implemented, as required.~~		
Section 7.4.2 Safety Criteria for Adjustment or Stopping Doses	***The text in this section is moved to Section 8.4.***		To avoid redundancy
Section 7.5 Criteria for Study Termination	The window of time for scheduling the visit will be based on a final projection of when the requisite ~~121~~ adjudicated events will have been accrued.	The window of time for scheduling the visit will be based on a final projection of when the requisite **127** adjudicated events will have been accrued.	Rationale 3
Section 8.4 Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	**[*Moved from Section 7.4.2 of Version 3*]** Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be **adjusted back** to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved. Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an **outcome** event, he or she should continue the regular visit schedule and continue taking investigational product as long as the **subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the** Investigator assesses it as safe. In general, subjects should be	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		strongly encouraged to both stay on investigational product and remain in the study until study termination.	
Section 8.4.1.1 Reasons for Additional Monitoring Related to Liver Chemistries	***Modification of 8.4.2.1 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.~~	**Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored.**	Clarified guidelines for subjects who develop elevations in liver chemistries. Language related to interruption of investigational product is now located in Section 8.4.1.2.
Section 8.4.1.2 Reasons for Investigational Product Interruption Related to	***Insertion***	**Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3x baseline (and >ULN)**	Clarified guidelines for subjects who develop elevations in liver chemistries.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Elevated Liver Chemistries		• **Total bilirubin >2x 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 AE information should also be collected and the subject 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 >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 investigative product and no other cause for the elevation is identified, it may be assumed that the**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		elevations were due to disease progression and the subject 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.** **If at any time a subject 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.** **Subjects who develop evidence of severe drug-induced liver injury, which is suspected to be causally related to the investigational product should be discontinued from investigational product and should not be rechallenged.**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		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 subjects 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 subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.** **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**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		adjudicated by the Hepatic Safety Committee (see Section 13.4).	
Section 8.4.1.3 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~	**8.4.1.3 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product **immediately,** but should continue with the study visit schedule. **As described in Section 12.1.11** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.11.**	Clarification regarding prolonged interruption in investigational product such as in the event of pregnancy.
Section 8.4.2.1 Liver Transplantation	***Text Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product*** Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.	**8.4.2.1 Liver Transplantation** Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.	The relocation of this statement from within Section 8.4.2 to 8.4.2.1 clarifies procedure to discontinue subjects who undergo a liver transplant, from investigational product but not study visits.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 8.4.3 Other Reasons for Discontinuation of Study or Investigational Product	8.4.2 Other Reasons for Discontinuation of Study or Investigational Product ~~Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).~~ The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or~~ cardiovascular events.	**8.4.3** Other Reasons for Discontinuation of **Study or** Investigational Product The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess **suspected major adverse**	Clarification of process

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.~~	cardiovascular events **(MACE) and liver-related clinical outcomes.** – **Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.18).** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	
Section 9.7.1 Visit Windows	Screening	Screening **See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.**	
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of ~~the study~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis.
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as noncirrhotic at Baseline per the criteria listed in Section 9.7.3.1 exhibits any signs or symptoms associated with progression to cirrhosis, as defined by the same criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy (centrally read) unless not medically indicated. Laboratory samples needed to obtain noninvasive scores of liver**	Details the assessment of progression to cirrhosis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis. **Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.** **Sites participating in the paired biopsy substudy must confirm progression to cirrhosis by biopsy as per the information outlined in protocol Addendum 2.** **All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	
Section 9.7.6 Screening Procedures	~~Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated~~ serum chemistry samples (at least 2 weeks apart) ~~to confirm~~ pretreatment ALP and total bilirubin values: ***Insertion*** • The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and	**Collection of 2 s**erum chemistry samples (**collected** at least 2 weeks apart**) during Screening is required for confirmation of the** pretreatment **serum chemistry values, including the** ALP and total bilirubin **used to determine eligibility**: • **When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Allows repeat assessments when baseline laboratory values are discrepant between Screening Visit 1 and Screening Visit 2.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN). • …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (~~selected~~ study sites ~~only~~), ***Insertion***	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5x** ULN and/or an ALP >**3x** ULN). • …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 **(at all** study sites **where the device is available**), **In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.**	
Section 9.7.7 Day 0 Procedures	• Perform ~~transient elastography (~~TE~~;~~ at ~~selected~~ study sites~~, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at ~~selected~~ study sites~~,~~ where device is available); • Perform an esophagogastroduodenoscopy (endoscopy; at ~~selected~~ study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.	• Perform TE at **all** study sites **with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at **all** study sites where **the device is** available); • Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where **device is** available) to assess the presence or absence of oesophageal varix/varices.	Clarifies use of TE and modifies the time during which an historic TE report remains valid. Clarifies the use of DEXA and endoscopy.
Section 9.7.8 Month 1 Procedures Section 9.7.10	9.7.10 Post-Titration visit Procedures ***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced	9.7.10 **1-Month** Post-Titration visit Procedures • Perform a physical examination. • In the event it is not feasible for the subject to return to the site for the above referenced	Physical Exams have been added one month after each dose adjustment for added safety monitoring. Options for safety monitoring assessments are provided

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
1-Month Post-Titration visit Procedures	procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements: ***Insertion (9.7.8)*** ***Insertion (9.7.10)***	procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit **laboratory** requirements: - **A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed**. - **A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed**.	when returning to the site presents significant burden on the subject.
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion*** ***Insertion in 9.7.11 (not 9.7.16)***	• **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).** • **Perform a physical examination**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis. Hepatic ultrasound has been increased to every 6 months to conform to AASLD and EASL guidelines for PBC patients with cirrhosis.
Section 9.7.12 Month 9 Procedures Section 9.7.14 Month 12 Procedures Section 9.7.16 Month 16 Continued	*...DEXA procedure to be done at* ~~selected~~ study sites ~~only~~,	*...DEXA procedure to be done at* **all** study sites **where the device is available**	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Follow-Up Procedures			
Section 9.7.14 Month 12 Procedures Section 9.7.17 Month 12 Follow-up Procedures Section 9.7.18 EOS/EOT	• Perform TE ~~(~~at ~~selected~~ study sites~~, where available) using the~~ Fibroscan® TE device. ***Additional edit in Section 9.7.18*** - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF ~~and remind the subject that fasting is required prior to all study visits~~.	• Perform TE at **all** study sites **with access to the** Fibroscan® TE device. - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.	Clarification
Section 10.3 Investigational Product Storage	~~The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical study 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.**	Updating temperature excursions language per Sponsor stability studies.
Section 11.1.2 Secondary Assessments	***Insertion***	• **Individual components of the primary endpoint.** • **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.**	Rationale 11

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in Addendum 2).** – **HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.**	Reflects addition of a biopsy substudy available to interested sites in Addendum 2.
	• Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ~~and~~ ELF, Fibroscan (and others as determined during the course of the study).	• Biomarkers, including **other** markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ELF, **and** Fibroscan (and others as determined during the course of the study). • **Clinical outcomes, including individual component of the primary endpoint (where available), liver transplant, and death will be compared to historical controls.** • **PK of OCA and its conjugates.**	
	• Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.	• Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.	
Section 12.1.3 Relationship of AEs to Liver Biopsy	***Insertion (new section)***	**The Investigator will document her/his opinion of relationship of an AE to liver biopsy using the criteria outlined in Table 9.** **Table 9: Relationship of Adverse Events to Liver Biopsy**	Added with the addition of liver biopsies for the confirmation of progression to cirrhosis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		Relationship / **Description** **Related** — **A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.** **Not Related** — **Any event that does not meet the above criteria.**	
Section 12.1.5.2 Reporting of Serious Adverse Events	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 ~~•Telephone: +1 858 964 1571~~ ~~Investigational new drug (IND) Safety Reports~~ ***Insertion***	If an SAE is reported by **email** or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible **Redacted medical record source documentation will be requested for all SAEs and emergency room visits.**	Updated to align with modified standard safety procedures. Added sentence regarding redacted medical records to align with Sponsor safety standards.
Section 12.1.6 Suspected Liver-Related Clinical Outcome Events	~~For~~ liver-related clinical outcome events ~~could~~ also meet the criteria of a SUSAR, ~~which would necessitate unblinding for expedited reporting, please refer to Section 11.1.2.4.~~	**Given that the** liver-related clinical outcome events **may** also meet the criteria of a SUSAR, **but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly, the Sponsor will not expeditiously report suspected liver-related 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 "study event" on the AE CRF and will be submitted for**	Updated to align with modified standard safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), ~~and~~ spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).	**adjudication to the Hepatic Outcomes Committee as described in Section 13.4**. The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 **or oesophageal varices haemorrhage**), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological or clinical progression to cirrhosis (preferred term: hepatic cirrhosis).**	
Section 12.1.8 Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	***Insertion (new section)***	**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 12.1.5.2.** **SAEs that occur in subjects 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 12.1.5.2.**	Updated to align with modified safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 12.1.9 Notification of Poststudy SAEs	All SAEs that occur within 30 days following the ~~cessation of investigational product~~, 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 12.1.~~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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours). ~~SAEs that occur more than 30 days after a subject has discontinued investigative product, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with investigative product, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.~~	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 12.1.**5**.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 12.1.5.2.	Updated to align with modified safety procedures and Sponsor standard language.
Section 12.1.10 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver**	Updated to align with modified standard safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		injury, indicating that liver injury was related to underlying liver disease.	
Section 12.1.11 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 8.4.1.3and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing or emailing~~ to ~~the Sponsor at +1 800 497 8521 or~~ sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use~~ of investigational product. ~~The subject may reinstate investigational product after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose~~ pregnancy is terminated early (planned or unplanned) ~~may be permitted to resume participation in the study if~~ termination of the pregnancy ~~is~~ confirmed by a serum β-hCG test ~~(see Section 8.4.1).~~	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** sae@interceptpharma.com **or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor**. **The subject 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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**	Updated to align with modified standard safety procedures and Sponsor standard language.

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td></td><td>reporting procedures described in Section 12.1.5 must also be followed.</td><td></td></tr>
<tr><td>Section 12.2.7
Laboratory Assessments</td><td>The list of laboratory analytes to be tested is shown in Table 1~~0~~.</td><td>The list of laboratory analytes to be tested is shown in Table 11, and the normal reference ranges for liver biochemistries are shown in Appendix C.</td><td>Added per Regulatory Authority request.</td></tr>
<tr><td>Section 12.2.7
Table 10 List of Laboratory Analytes</td><td><table><tr><td>~~Measurement of Liver Fibrosis~~</td><td>~~Fibroscan~~</td></tr><tr><td>~~Bone Density Assessment~~</td><td>~~DEXA~~</td></tr><tr><td>Other</td><td>Insertion</td></tr></table></td><td>Deletion<table><tr><td>Other</td><td>OCA-glucuronide</td></tr></table></td><td>Measurements of liver fibrosis are captured in a different section.

OCA-glucuronide was listed in the text but missing from the table.</td></tr>
<tr><td>Section 13
Statistical Methods</td><td>A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior ~~to study database lock~~, propensity score determination, and unblinding of the double-blind subject treatment assignments.</td><td>A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the first interim analysis, propensity score determination, and unblinding of the double-blind subject treatment assignments.</td><td>Reflects addition of interim analyses to the study protocol.</td></tr>
<tr><td>Section 13.1.1
Analysis Populations</td><td>~~• The Randomized Population will include all randomized subjects~~

Insertion</td><td>Deletion

• The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.</td><td>Rationale 12</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.1.1 Comparability of Historical Controls	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria ~~where possible~~.	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. **Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8**.	Clarifies the use of propensity scores in the assessment of the historical control population.
Section 13.1.2.1 Sample Size Monitoring	13.1.2.1 Sample Size ~~Re-Estimation Plan~~ Therefore, ~~starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups. ~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.~~	13.1.2.1 Sample Size **Monitoring** Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of **127** adjudicated events for the final analysis in the combined groups. ***Deletion***	Clarifies the ongoing monitoring of event rate and sample size.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~		
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion (new subsection)***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between biochemistry including ALP and bilirubin with clinical outcomes will be assessed and the clinical benefit of OCA using biochemistry as a surrogate endpoint will be evaluated. Detailed analysis will be described in the SAP.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA using biochemistry as a surrogate endpoint for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
Section 13.1.8 Supportive Analysis	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment. ~~Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process~~	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, **which serves as an external control for supportive analysis**. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment **between the treated subjects and the matched natural history subjects**. **A** full range of covariates across which the treatment and historical controls might differ **will be considered to mitigate potential bias**.	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis. Clarifies the use of the historical controls as an external control in supportive

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~is to successfully mitigate potential bias, it has to be done considering~~ ~~a~~ full range of covariates across which the treatment and historical controls might differ. Only covariates and not outcome variables will be included in the propensity score estimation. ~~Therefore, there is no chance of biasing,~~ to avoid biased results that are in favor of one treatment. The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	Only covariates and not outcome variables will be included in the propensity score estimation **to avoid biased** results **that are** in favor of one treatment. **The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.** **A third-party statistician(s) will perform the propensity score modeling and matching. This third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses.** The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	• ~~Time to hepatocellular carcinoma~~ ***(Text from Section 13.1.9 [Alternative Primary Analysis] modified and included in this section)*** ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new~~ primary efficacy ~~analysis will become the comparison of~~ all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause~~) (see Section 13.1.2.1~~). similar statistical methodology as specified above ~~in Section 13.1.8 for supportive analyses will be utilized~~. ~~The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct** based on **the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised** primary efficacy analysis. **This analysis would compare** all subjects in **the** OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), **using** similar statistical methodology as specified above. **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
Section 13.1.9 Handling of Dropouts or Missing Data	***Insertion***	**In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.**	Clarification of statistical analyses to address missing data.
Section 13.1.11 Examination of Subgroups	The primary and secondary efficacy endpoints will be analyzed for subject subgroups **(eg, age, sex, and race)** based on the ITT population. ***Insertion***	The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. **The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)** • **Early (normal albumin and normal bilirubin)** • **Moderate (abnormal albumin or abnormal bilirubin)** • **Advanced (abnormal albumin and abnormal bilirubin)** **The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.**	Added per Regulatory Authority request.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Monotherapy in patients who are intolerant or non-responsive to UDCA** • **Elderly patients** **Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.** **Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.**	
Section 13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs, and/or loss of subjects to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% (64 events) and 75% (96 events) of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for**	Two Interim Analyses have been added to the protocol.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		efficacy) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.	
Section 19 List of References	***Insertion***	**Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Digestive and Liver Disease. 2015a;47(11):924-6.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.** **Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6α-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-3572.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	Additional relevant references were added.
Appendix A	Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg	Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg	Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment	OCA or matching placebo once daily, based on tolerability.	OCA or matching placebo once daily, based on tolerability **and biochemical response**.	
Appendix B List of Study 747-302 Outcome Events	***This Appendix with the following information has been deleted.*** ~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~		Redundant; Information is contained within the protocol.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Hepatocellular carcinoma~~		
Appendix C Reference Laboratory Values from Central Laboratories	***Insertion (new appendix)***	***Appendix containing reference laboratory values from central laboratories added.***	Added per Regulatory Authority request.

APPENDIX J. SUMMARY OF CHANGES: PROTOCOL VERSION 4 TO PROTOCOL VERSION 5 (DATED 04 JAN 2018)

Rationale

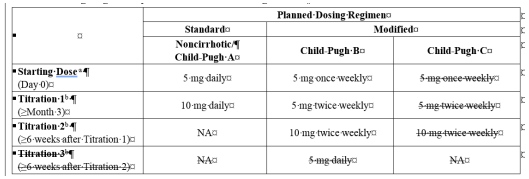
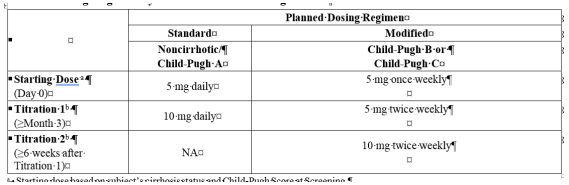
Protocol 747-302 was revised to include the following information:

- 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 United States Package Insert dosing guidelines. Titration is now only based on tolerability and not CP score.
- 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 diagnosed 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 5. Revised and new text in Version 5 is indicated in bold font, and the text deleted from Protocol Version 4 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below. Section numbers and names in column 1 refer to protocol Version 5 unless otherwise noted.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Sponsor's approval	PPD PhD PPD Clinical Development Intercept Pharmaceuticals, Inc.	PPD PhD PPD Clinical Development Intercept Pharmaceuticals, Inc.	Change in title
Study Personnel Contact Information	~~Contact:~~ PPD ~~MD, Medical Director, Drug Safety,~~ ~~Intercept Pharmaceuticals~~ ~~Mobile:~~ PPD ~~(Pacific time zone)~~ ~~Telephone:~~ PPD ~~Email:~~ PPD	Primary Contact: PPD **MD, MPH|** **Senior Medical Director / Medical Affairs** **Syneos Health | Chapel Hill, NC 27514 |U.S.A.** **Tel:** PPD **Mobile:** PPD PPD **Secondary Contact:** PPD **DO, MSPH** **Senior Medical Director** **Intercept Pharmaceuticals, Inc. (Intercept)** PPD	Updated medical monitoring contact information
Synopsis, Phase of Development	Phase 4:	Phase 4: **US, Canada, and the EU** **Phase 3b: All other regions**	Clarified that the phase of the study has been changed from "3b" to "4" to reflect that this is a post-marketing 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.
Synopsis, Methodology,	…Subjects classified as Child-Pugh Class B ~~should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability and biochemical response.~~	Subjects classified as Child-Pugh Class B or Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA **or** matching placebo twice	To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~Subjects classified as~~ Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly, based on tolerability and biochemical response	weekly **(at least 3 days apart)**, based on tolerability and biochemical response.	
Synopsis, Methodology, Table -Planned Dosing Regimen by Cirrhosis and Child-Pugh Score, Section 7.3, Planned Dosing Regimen, Table 3		 a Starting dose based on subject's cirrhosis status and Child-Pugh Score at Screening. b Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study c **Dosing per the twice weekly schedule must be at least 3 days apart**	Titration #3 is no longer applicable to study. To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Synopsis, Criteria for Evaluation; Secondary Objectives	Safety and tolerability Including the following: Treatment-emergent adverse events Clinical laboratory values	Safety and tolerability Including the following: Treatment-emergent adverse events **including adverse events of special interest** Clinical laboratory values	Per FDA request
Synopsis, Statistical Methods, Safety Analysis,	Safety data, including AEs, vitals, electrocardiogram	Safety data, including AEs, **AEs of special interest including pruritus and hepatic safety**, vitals, electrocardiogram…	Per FDA request
Section 5.1, Overview of Primary Biliary	In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication	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 747-302 is**	Clarified that the phase of the study has been changed from "3b" to "4" to reflect that this is a post-marketing

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Cholangitis and Obeticholic Acid		**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**	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
Section 5.4, Clinical Experience with Obeticholic Acid	As of ~~31 Jan~~ 2017, approximately ~~2186~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~525~~ subjects had PBC, ~~686~~ subjects had NASH, 41 subjects had diabetes mellitus/nonalcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~52~~ subjects had primary sclerosing cholangitis, and ~~5~~ subjects 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** subjects had PBC, **1141** subjects had NASH, 41 subjects had diabetes mellitus/nonalcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **73** subjects had primary sclerosing cholangitis, and **6** subjects had biliary atresia	Updated number of subjects exposed to OCA
Section 5.6, Importance of Monitoring of Disease Progression	Insertion	**Given PBC is a chronic, progressive liver disease, it is important that subjects with PBC are closely monitored to ensure early identification of potential disease progression to cirrhosis, decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve subject oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules based laboratory monitoring. Subjects will be monitored for potential hepatic injury and/or decompensation and progression to cirrhosis (Section 7.5). Criteria for implementing**	Per FDA response

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 7.6 and Section 7.7. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.	
Section 5.7, Summary of Known Potential Risks with OCA	…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, ~~but~~ with ~~a much lower~~ frequency ~~than that~~ observed in subjects 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 subjects 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 (HDL)~~ and an increase in low	**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. One case was reported in a subject with no evidence of cirrhosis at baseline, while the second case was reported in a subject with cirrhosis and hepatic impairment at baseline. 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**	Per FDA Response Updated section to include SUSARS

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	density lipoprotein (LDL). ~~Notably, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA treated subjects with the exception of a modest transient and early rise after initiation of treatment~~. Refer to the ~~Investigator's Brochure~~ (IB) for additional information regarding the known potential risks with the investigational product.	**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 providing further support for the lack of safety concern and positive benefit-risk profile of OCA.** **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**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		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	
Table 1, Schedule of Procedures, Screening to Month 12	Insertion	**Added column for M2 and following procedures at the visit** • **Physical Exam** • **Child-Pugh Assessment** • **Adverse Events** • **Prior/Concomitant Medications** • **IP accountability/Compliance** • **Dosing Diary** • **Chemistry/Hematology/Coagulation** • **Review Progression to Cirrhosis Algorithm**	Added to satisfy requirement for monthly visits following any titration

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~1 Month~~ Post-Titration Visit	Post-Titration Visit**s**	
Table 1, Schedule of Study Procedures, Screening to Month 12; and Table 2, Schedule of Study Procedures Year 2 Through End of Study	Insertions	Added the following procedures • **Gallbladder Assessment** *(Table 1 only)* • **Amylase and Lipase** (if subject experiences acute pancreatitis or cholecystitis) • **Review Progression to Cirrhosis Algorithm**	Added per FDA request
Table 1, Schedule of Events, Screening to Month 12; and Table 2, Schedule of Study Procedures Year 2 Through End of Study	• ~~Assessments for Mayo Risk Score~~ • ~~DEXA~~ • ~~Blood samples for future analysis~~		Central lab will calculate value Procedures deleted to streamline collection of laboratory samples
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote b	Post-Titration visits must be performed 1 month (+ 1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up titration to 10 mg OCA or matching placebo~~, or after ≥3 months at a decreased dose or frequency~~.	Post-Titration visits must be performed 1 month (+ 1 week) **and 2 months** (+1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child Pugh B and Child-Pugh C hepatic impairment. **See Appendix A for additional guidance.** In subjects following the standard dosing regimen, the post-titration visit must be performed **1 month (+ 1 week) and 2 months (+1 week)** only after the first up titration to 10 mg OCA or matching placebo.	Added to satisfy requirement for monthly visits following any titration

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Table 1, Schedule of Study Procedures, Screening to Month 12, *previous* footnote f	~~Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the eCRF.~~	Deletion	MRS score will be calculated by central lab.
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote k	~~DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure~~	deleted	Procedures deleted to streamline collection of laboratory samples
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote k	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.~~	Ultrasound will be conducted to enhance HCC surveillance **and for gallbladder assessment at Screening. If ultrasound was not performed at Screening and the historic ultrasound is >3 months from Day 0, perform a hepatobiliary ultrasound at the Day 0 visit.**	Agreement with FDA to perform gallbladder assessments at screening.
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote p	The subject 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.	The subject 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. **MELD and MRS values will be calculated based on serum chemistry and coagulation values at each visit.**	MELD and MRS removed as line items. Central lab will calculate these values.
Table 1, Schedule of Study Procedures, Screening to Month 12,	~~Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis~~	Deletion	Procedures deleted to streamline collection of laboratory samples

Section	Original Text (Amendment 4, 10 May 2017)		Revised Text (Version 5, 04 Jan 2018)		Justification for Change
footnote l, Table 1, footnote w					
Table 2, Schedule of Study Procedures Year 2 Through End of Study	Column header: ~~1 Month~~ Post-Titration Visit[a],		Post-Titration Visits[a]		Added to satisfy requirement for monthly visits following any titration, requirement to assess Child-Pugh at every visit.
Table 2, Schedule of Study Procedures Year 2 Through End of Study	~~Assessment for Mayo Risk Score~~[e] ~~DEXA~~ ~~Blood Sample for Future Analysis~~		Deletion		MRS score will be calculated by central lab.
Table 2, Schedule of Study Procedures Year 2 Through End of Study	Visit Windows (+/-)c	Year 2 Through End of Study	Visit Windows (+/-)c	Year 2 Through End of Study	Added per FDA
	Insertion		**Amylase and Lipase**	**Sample to be collected if the subject experiences acute pancreatitis or cholecystitis**	
			Review Progression to Cirrhosis Algorithm		
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote a	~~In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.~~ Post-~~titration visits~~ must be performed 1 month ~~±~~ 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment.		Post-**Titration Visits** must be performed 1 month **(**±1 week**) and 2 months (±1 week)** after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. **See** Appendix A **for additional guidance. In subjects following the standard dosing regimen, the Post-Titration visit must only be performed 1 month (±1 week) and 2 months (±1 week) after the first up-titration to 10 mg OCA or matching placebo.**		Added to satisfy requirement for monthly visits following any titration, requirement to assess Child-Pugh at every visit.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote e	~~Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF~~		MRS score will be calculated by central lab
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote g	~~Height will be collected at this visit~~		
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote j	~~DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available~~		Procedure deleted
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote m	The subject 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.	The subject 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. **MELD and MRS values will be calculated based on serum chemistry values at each visit.**	MELD and MRS removed as line items. Central lab will calculate these values.
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote s	~~Please refer to Section for description of the blood sample to be collected for future analysis~~		Procedure deleted
Section 7.3, Planned Dosing Regimen	Insertion	**Non-Cirrhotic or Child-Pugh A** **…** **Cirrhotic or Child-Pugh B or C** **Subjects with cirrhosis (see Section 7.5.4) and classified as Child-Pugh Class B or Child-Pugh**	Heading and text added for additional clarity.

<table>
<tr><th>Section</th><th>Original Text (Amendment 4, 10 May 2017)</th><th>Revised Text (Version 5, 04 Jan 2018)</th><th>Justification for Change</th></tr>
<tr><td></td><td></td><td>Class C will follow a modified dosing regimen, initiating 5 mg OCA or matching placebo once weekly. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.
Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).
The dosing regimen should be determined as described shown in Table 13 Appendix A.
Investigators should follow the dosing/titration schedule as shown described in Section 7.4 and Appendix A.</td><td></td></tr>
<tr><td>Section 7.3, Planned Dosing Regimen, Table 3</td><td>▪ Table 5: → Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score¶
<table><tr><th rowspan="2">▪ Original Status¤</th><th colspan="3">New Status¤</th></tr><tr><th>Noncirrhotic OR¶ Child-Pugh A¤</th><th>Child-Pugh B¤</th><th>Child-Pugh C¤</th></tr><tr><td>Noncirrhotic or¶ Child-Pugh A¤</td><td>No Change¤</td><td>~~10 mg daily~~ → 5 mg ~~daily~~¶ ~~5 mg daily~~ → No change or 10 mg twice weekly[b]¤</td><td>5 mg or 10 mg daily → 10 mg twice weekly[b]¤</td></tr><tr><td>Child-Pugh B¤</td><td>5 mg daily → 10 mg daily¤</td><td>No Change¤</td><td>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~~¤</td></tr><tr><td>Child-Pugh C¤</td><td>10 mg twice weekly → 5 mg daily¤</td><td>~~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¤</td><td>No Change¤</td></tr></table></td><td>▪ Table 3: → Planned Dosing Regimen by Cirrhosis and Child-Pugh Score¶
<table><tr><th rowspan="2">▪ ¤</th><th colspan="2">Scheduled Dosing Regimen¤</th></tr><tr><th>Standard¤</th><th>Modified¤</th></tr><tr><td>▪ Starting Dose [a] ¶ (Day 0)¤</td><td>Noncirrhotic/¶ Child-Pugh A¤
5 mg daily¤</td><td>Child-Pugh B or¶ Child-Pugh C¤
5 mg once weekly¶ ¤</td></tr><tr><td>▪ Titration 1[b] ¶ (≥Month 3)¤</td><td>10 mg daily¤</td><td>5 mg twice weekly[c]¶ ¤</td></tr><tr><td>▪ Titration 2[b] ¶ (≥6 weeks after Titration 1)¤</td><td>NA¤</td><td>10 mg twice weekly[c]¶ ¤</td></tr></table>[a] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening.¶
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4).¶
[c] Dosing per the twice weekly schedule must be at least 3 days apart.¶</td><td>To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.</td></tr>
</table>

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.3, Planned Dosing Regimen, Table 4	~~Table 4: Determination of Dosing Regimen~~ ~~Cirrhosis?~~ | No | ~~Yes~~ | Yes | ~~Yes~~ ~~Child-Pugh Score~~ | Any | A | B | ~~C~~ ~~Dosing Regimen~~ | Standard | ~~Modified for Child-Pugh B~~ | ~~Modified for Child-Pugh C~~	**Table deleted**	To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Section 7.4, Dose Titration Criteria	... Up-titrations may only occur to the maximum dose and frequency for each dosing regimen as defined in Section 7.3.	... Up-titrations may only occur to the maximum dose and frequency for each dosing regimen as defined in Section 7.3. **A 1-Month and 2 Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.7).**	Clarify dosing assessments.
Section 7.4, Dose Titration Criteria, Dose Titration due to Change in Cirrhosis or Child-Pugh Score	Changes to the dosing regimen ~~are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. provides an overview of the possible changes in dosing regimen due to changes in cirrhosis or Child-Pugh Score~~. ... Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and ~~should not necessarily result in~~ a change to the dosing regimen ~~Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration~~	…Changes **in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change** to the dosing regimen ... Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters (**eg, increase in vitamin K resulting in change in INR**) should be documented appropriately and **discussed with the Medical Monitor before any continuation** or change to the dosing regimen	Clarify that changes in CP scores should be discussed with medical monitor.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~assessment requirements for dosing as described in Section .~~ Child-Pugh Scores will be calculated at all quarterly study visits	Child-Pugh Scores will be calculated **during screening**, at **each scheduled** study visits**, and at unscheduled visits in the event of signs or symptoms of suspected hepatic injury or decompensation are present.**	
Section 7.4.1, Pre-Titration Tolerability Assessment Requirements	Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the ~~1 Month~~ Post- Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are…	Safety laboratory results obtained at the visit (for titration at Month 3) or at the Post- Titration Assessment visit**s** (for titration prior to or at the subsequent quarterly visit) are…	Added to satisfy requirement for monthly visits following any titration
Section 7.5, Monitoring and Management of Potential Hepatic Injury and/or Disease Progression	Insertion	**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 (Table 1). Child Pugh Scores should only be applied in patients who demonstrate progression to cirrhosis based on criteria presented in Section 7.5.4. 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 the assessments of signs and symptoms of hepatic injury and liver biochemistry, the investigational product may be interrupted or discontinued per criteria discussed in Section 7.5.2 and Section 7.5.3, and close monitoring procedures will be implemented (Section 7.7).**	Per FDA response, language added to provide guidance for monitoring disease progression due to potential hepatic decompensation.

Section 7.5.1, Signs and Symptoms of Hepatic Injury or Decompensation	Insertion	**7.5.1. Signs and Symptoms of Hepatic Injury or Decompensation** **Subjects 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 subject evaluation** **Other Symptoms:** • **Worsening of renal function or likely dehydration** **Healthcare Provider (HCP) Interactions:**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		• **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 7.5.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.5 (3) triggering of investigational product interruption or discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 12.1.5.1 and Section 12.1.5.2), and (5) contact with the Medical Monitor.**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.5.2, Liver Biochemistry Assessments for Suspected Hepatic Injury or Potential Hepatic Decompensation	Insertion	**Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of subjects for potential hepatic injury or hepatic decompensation. These assessments will be performed at:** • **Each protocol-specified visit** • **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 subject 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 subject evaluation (depending on the repeat result) are summarized in Table 5.** **Figure 2: DILI Management Algorithm.** **Table 5: Liver Laboratory Criteria for Monitoring of Suspected Hepatic Injury or Potential Hepatic Decompensation and Criteria for Interruption or Discontinuation of Investigational Product.**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		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 subjects' 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.	
Section 7.5.3, Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events	Insertion	**Subjects will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for the monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 6.** **Investigational product should be discontinued permanently if the subject received a liver transplant or experiences multi-organ failure as defined in Table 6, Part A). Subjects should continue to return for scheduled study visits for safety follow up.** **Subjects who experience other potential hepatic decompensation events defined in Table 6, Part B should be closely monitored until normalization or stabilization. Subjects may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.** **Table 6: Criteria for Monitoring Potential Hepatic Decompensation Events and Interruption / Discontinuation of Investigational Product**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.5.4, Assessing Cirrhosis		*Section and subsections were moved from previous Section 9.7.3 and subsections.*	Content moved as it supports new content described above.
Section 7.5.5, Child-Pugh Score		*Section was moved from previous Section 9.7.4.*	
Section 7.5.5.1, Mayo Risk Score		*Section was moved from previous Section 9.7.5.*	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.6, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	Insertion	**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 8), investigational product should be initiated at a lower dose and subjects 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 8. Subjects that 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 terminate at the time when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Table 8, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.** **Table 8: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge.**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

Section 7.7, Close Observation	Insertion	**If investigational product is interrupted or discontinued as described in Section 7.6, subjects 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 subject 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 subject 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 subject 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 7.5.1, Section 7.5.2, and Section 7.5.3. These cases need to be discussed with the Sponsor's medical monitor:** • **Repeating liver enzyme and serum bilirubin tests as described in Section 7.5.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

		drug has been discontinued and the subject 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 subject 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 (HEV) when assessing for hepatic decompensation as infection with HEV in patients with chronic liver diseases such as PBC may rapidly worsen with signs and symptoms similar to drug induce liver injury (Kumar 2013)**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		• **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. Subject Withdrawal Criteria	~~Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be adjusted back to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.~~ ~~Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination~~.	**Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from** investigational product are expected to continue in the study and **should** follow the regular visit schedule **for the duration** of the study**. See Section 7.6 for withdrawal criteria related to potential hepatic injury and/or decompensation; including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.1 below.**	Section updated to conform with FDA response.
Previous Section 8.4.1.1, Reasons for Additional Monitoring Related to Liver	~~Subjects 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. Subjects with persistent elevations (eg, additional lab testing per~~		Replaced with updated DILI text in Section 7.5.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Chemistries (Version 4)	~~Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored~~		
Previous Section 8.4.1.2, Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries (Version 4)	~~Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:~~ ~~• AST and/or ALT >3x baseline (and >ULN)~~ ~~• Total bilirubin >2x 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 AE information should also be collected and the subject 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 >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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~~		Replaced with updated DILI text in Section 7.5.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~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 study medication and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject 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.~~ ~~If at any time a subject 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.~~		

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~Subjects who develop evidence of severe drug-induced liver injury, which 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 subjects 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 subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.~~ ~~The Medical Monitor must be contacted in all cases of persistent liver biochemistry elevations.~~		

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~All hepatic injury events, regardless of relationship to investigational product, will be adjudicated by the Hepatic Safety Committee (see Section 13.4)~~		
Previous Section 8.4.1.3,Pregnancy (Version 4)	~~If a female subject becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 12.1.11 pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 12.1.11.~~		Addressed in Table 8 in Section 7.6.
Previous Section 8.4.2.1, Liver Transplantation (Version 4)	~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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 discussed in Table 8 in Section 7.6
Section 9.7.1, Visit Windows	Post-Titration Visit: 1 month (+1week [7 days]) from date of titration ~~or after ≥3 months at a decreased dose or frequency~~	Post-Titration Visit: 1 month **and 2 months** **(**±1week [7 days]) from date of titration	Added to satisfy requirement for monthly visits following any titration
Previous 9.7.3, Assessing Cirrhosis (Version 4)		*Section and subsections were moved to earlier in the document (7.5.4 and subsections).*	Content moved.
Section 9.7.3, Screening Procedures (1 to 8	**…**	…	Agreement with FDA to perform gallbladder assessments at screening.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Weeks prior to Day 0)	• ~~Perform assessment for calculation of Mayo Risk Score~~ • 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 Visit 2~~, and a report/adequate data are available, a pretreatment ultrasound at ~~Screening Visit 2~~ is not required. … Results from the screening ultrasound ~~should~~ be reviewed to assess possible exclusion criteria prior to randomization. • ~~Record current~~ concomitant medications • ~~In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (at all study sites where the device is available), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.~~	• Perform an ultrasound for HCC surveillance and **gallbladder assessment** (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within **3** months **of the planned Day 0 visit**, and a report/adequate data are available, a pretreatment ultrasound is not required. … Results from the screening ultrasound **must** be reviewed to assess possible exclusion criteria, prior to randomization. • **Review and record prior and** concomitant medications	DEXA removed to streamline laboratory procedures.
Previous Section 9.7.4, Child-Pugh Score (Version 4)		*Section was moved to earlier in the document (7.5.5).*	Content moved.
Section 9.7.4, Day 0 Procedures (Randomization)	… ~~Conduct a DEXA bone density scan (at all study sites where the device is available); document~~	**…** • **If hepatobiliary ultrasound for HCC screening and gallbladder assessment was not performed**	Per FDA request

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed~~. … • Obtain blood samples for: – OCA, C4, and fibroblast growth factor-19 (FGF-19) – Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF]) – Genetics (see Section 11.1.2.3) – ~~Blood sample for future analysis (refer to Section 11.1.2.3)~~	**at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound.** … Obtain blood samples for: – OCA, C4, and fibroblast growth factor-19 (FGF-19) – Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF]) – Genetics (see Section 11.1.2.3) • **Perform assessments for calculation of Child-Pugh Score**	
Previous Section 9.7.5, Mayo Risk Score (Version 4)		*Section was moved to earlier in the document (7.5.5.1).*	Content moved.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 9.7.5, Month**s** 1**, 2** Procedures	... • Review and record concomitant medications. … In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit laboratory requirements: -At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the ~~Month 1~~ visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. The subject must also be contacted via telephone at the ~~Month 1~~ visit	... • Review and record **prior and** concomitant medications. … • **Perform assessments for calculation of Child-Pugh Score.** • **Review progression to cirrhosis algorithm.** … In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 **and Month 2** visit laboratory requirements: -At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -If all other options for the collection of the Month 1 **and Month 2** laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. **The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern.** The subject must also be contacted via	Month 2 added to section satisfy requirement for monthly visits following any titration and assess CP score per FDA request.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed.	telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -A physical examination should be performed at the Month 3 visit if an onsite Month 1 **or Month 2** visit was not performed.	
Section 9.7.6 Month 3 Procedures;	Insertions.	… • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications.	Per FDA request
Section 9.7.7, Post-Titration Visit Procedures	… • Review and record concomitant medications. … If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit	… • Review and record **prior and** concomitant medications. **…** • **Perform assessments for calculation of Child-Pugh Score.** • **Review progression to cirrhosis algorithm.** **…** If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. **The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern.** The subject	per FDA request

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	time point to assess AEs, review concomitant medications, and assess investigational product compliance;	must also be contacted via telephone at the Post-Titration Visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;	
Section 9.7.8, Month 6 Procedures	… • ~~Perform assessment for calculation of Mayo Risk Score.~~ … • Review and record concomitant medications. … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – ~~Blood sample for future analysis (refer to Section 11.1.2.2)~~	… • **Review progression to cirrhosis algorithm.** **…** • Review and record **prior and** concomitant medications. … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF)	
Section 9.7.9 Month 9 Procedures	… • Review and record concomitant medications … • ~~In preparation for the DEXA bone density scan to be done at the Month 12 visit (at all study sites where the device is available),~~	… • **Review progression to cirrhosis algorithm** • Review and record **prior and** concomitant medications …	per FDA request. Procedure deleted.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan~~		
Section 9.7.11 Month 12 Procedures	… ~~Perform assessment for calculation of Mayo Risk Score.~~ … • ~~Conduct a DEXA bone density scan (at all study sites, where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable~~ … • Review and record concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3) ~~Blood sample for future analysis (refer to Section 11.1.2.3)~~	**…** • **Perform assessments for calculation of Child-Pugh Score** • **Review progression to cirrhosis algorithm** **…** • Review and record **prior and** concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3)	Per FDA request. Procedures deleted.
Section 9.7.12, Month 3 and Month 9 Continued Follow-Up	Insertions	**…** • **Review progression to cirrhosis algorithm** **…**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Procedures (±2 weeks)		• Review and record **prior and** concomitant medications	
Section 9.7.13, Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])	• ~~Perform assessment for calculation of Mayo Risk Score.~~ • Perform assessments for calculation of Child-Pugh Score. … • Review and record concomitant medications … • Obtain blood samples for: – Markers of hepatic fibrosis and/or inflammation (including ELF). – ~~Blood sample for future analysis (refer to Section 11.1.2.3).~~ • ~~At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (at all study sites where the device is available), subjects who are taking calcium supplements~~	• Perform assessments for calculation of Child-Pugh Score. • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications … • Obtain blood samples for: – Markers of hepatic fibrosis and/or inflammation (including ELF).	per FDA request. Procedures deleted

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.~~		
Section 9.7.14, Month 12 Continued Follow-up Procedures (Annually [±2 weeks])	• ~~Perform assessment for calculation of Mayo Risk Score~~ … • ~~Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable~~. … • Review and record concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3) – ~~Blood sample for future analysis (refer to Section 11.1.2.3~~	**…** • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3)	per FDA request. Procedures deleted

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 9.7.15, Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent	Table 9, footnote c … ~~No~~ Additional data (~~e.g. AE~~, concomitant ~~medication, etc) data will~~ be collected, ~~except as indicated in Section~~ . Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing. … • ~~Perform assessment for calculation of Mayo Risk Score~~ … • ~~Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.~~ • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) • ~~Blood sample for future analysis (refer to Section 11.1.2.3~~	Table 9, footnote c … Additional data **such information on concurrent medical conditions, co-morbidities, relevant and** concomitant **medications may** be collected **to help facilitate adjudication of these post-study events.** Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing. … • **Review progression to cirrhosis algorithm** … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF)	
Section 11.1.2.3, Other Exploratory Evaluations	• ~~Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood~~	Deleted	Procedure deleted

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.~~		
Section 12.1.1.1, Adverse Event	Insertions	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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. **For reporting purposes, pregnancy is not considered an AE** **Subjects 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 the or whites of eyes, and bruising easily.**	Per FDA request
Section 12.1.1.4, Adverse Events of Special Interest	Insertion	**The following decompensation events are adverse events of special interest. A subset of these events are also individual components of the primary endpoint (Section 11.1.1).**	Per FDA request

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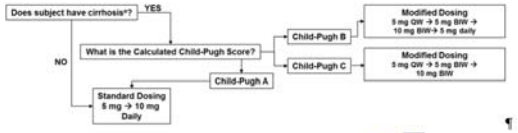
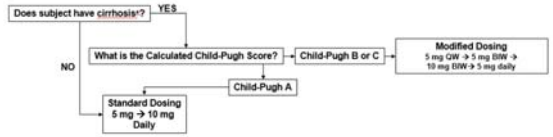
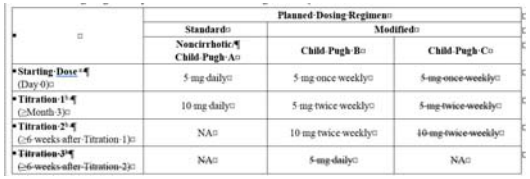
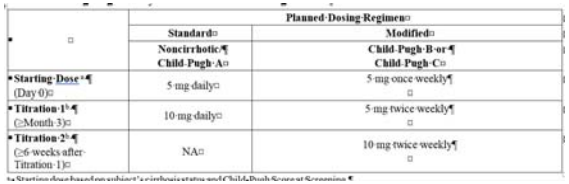
		• **Variceal bleeding or recurrent variceal bleeding documented by endoscopy OR patient presenting with anemia or melena (hemoglobin drop ≥2 gm/dL) and found to have varices documented by endoscopy, irrespective of hospitalization or requirement of blood transfusion.** • **Gastrointestinal bleeding as 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**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		– **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 12.1.5.1, 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 subject.**	Per FDA request
Section 12.1.10, Follow-up of AEs and SAEs	… Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the CRF. Note that longer follow-up can sometimes reveal an off-drug repetition.	**Drug-Induced Liver Injury or Disease Progression** … Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results **from drug induced liver injury follow-up** should be recorded in the **e**CRF. Note that longer follow-up can sometimes reveal an off-drug repetition… **Cholecystitis or Pancreatitis** **At the time of consent for new subjects (or re-consent to the protocol amendments for ongoing subjects), subjects will 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. Subjects will 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 will be instructed to promptly bring subjects into the clinic to undergo**	

Section	Original Text (Amendment 4, 10 May 2017)		Revised Text (Version 5, 04 Jan 2018)		Justification for Change
			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 will be monitored monthly for 3 months after onset of symptoms, irrespective of whether a diagnosis of cholecystitis and or pancreatitis is confirmed. Results should be recorded promptly in the eCRF.**		
Section 12.2.5, Dual Emission X-Ray Absorptiometry	~~12.2.5. Dual Emission X-Ray Absorptiometry~~ ~~A bone density assessment will be done using the DEXA scan.~~		Deleted		Procedure deleted
Section 12.2.6, Laboratory Assessments	Subjects will be instructed to attend ~~each of~~ their study visits (except Screening) in a fasted state,		Subjects will be instructed to attend **any** study or **unscheduled laboratory** visits (except Screening) in a fasted state,		Clarify subject should fast for all lab visits.
Section 12.2.6, Laboratory Assessments, Table 13	Laboratory Assessment	Analyte	Laboratory Assessment	Analyte	Labs added per FDA request
			Markers of Cholecystitis and Pancreatitis	**amylase and lipase**	

Section	Original Text (Amendment 4, 10 May 2017)		Revised Text (Version 5, 04 Jan 2018)		Justification for Change
	~~Blood Sample for Future Analysis~~	~~PBC autoantibodies and other cytokines and interleukins TBD~~			Procedure deleted
Section 12.2.6, Laboratory Assessments,	MELD scores, Child-Pugh score, ~~and MRS~~ will be calculated at screening, and ~~at quarterly (MELD and Child-Pugh scores) or semi-annual (MRS)~~ visits based on serum chemistry and coagulation.		MELD scores **and** Child-Pugh score will be calculated at screening, and at **all** visits based on serum chemistry and coagulation.		Clarify subject should fast for all lab visits
Section 13.2.1, Safety Analyses, Adverse Events	Insertion		**Adverse events of special interest as described in Section 12.1.1.4 will be summarized for each treatment group. In addition, each event is a component of the primary endpoint, and will be summarized as secondary endpoints as described in Section 13.1.4.**		Per FDA request.
Section 13.4, Adjudication Committees	All suspected liver-related clinical outcomes, 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~~		All suspected liver-related clinical outcomes and MACE/Expanded MACE 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 **2** 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 Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the suspected events to be		There is no longer a need for the Hepatic Safety Committee given the updated guidance for the Investigator.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	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,	adjudicated, supply of source documentation to the committee,	
References		**Kumar A, Saraswat V. Hepatitis E and Acute-on-Chronic Liver Failure. J Clin Exp Hepatol. 2013 Sep;3(3):225-30. doi: 10.1016/j.jceh.2013.08.013. Epub 2013 Sep 16** **Banks O, Bollen T, Dervenis C, et al. Classification of acute pancreatitis02012: 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.** **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.**	
Appendix A, Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment	… ~~Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment~~ ~~An overview of the modified dosing regimen for subjects with Child-Pugh Class B or Child-Pugh Class C is presented in and .~~ ~~Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5 mg OCA or matching placebo once weekly for at~~	**Subjects with cirrhosis and classified as Child-Pugh B or Child-Pugh C at Screening will follow a modified dosing schedule initiating 5 mg OCA or matching placebo once weekly as described in Figure 3. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for**	Deleted overview section and replaced with text

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability and biochemical response. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly.~~	**a minimum of at least 6 weeks, and meet the dose titration criteria, should up titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly (Table 14). Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).**	
Appendix A, Figure 3			Same dosing scheme for CP-B and CP-C subjects.
Appendix A, Table 14			Titration #3 is no longer applicable to study. To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Appendix A	~~Modified Dosing Regimen for Subjects with Child-Pugh B Hepatic Impairment~~ ~~Subjects with cirrhosis and classified as Child-Pugh BC at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in . After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of~~		

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~at least 6 weeks, and meet the dose titration criteria, should up-titrate to twice weekly dosing with 10 mg OCA or matching placebo. Subjects with at least 6 weeks of twice weekly dosing at 10 mg OCA or matching placebo, and meeting dose titration criteria, should up-titrate to the maximum allowed dose of 5 mg OCA or matching placebo once daily.~~ ~~Investigators may decrease the dosing frequency (back to once or twice weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).~~		
Appendix A, Dose Titration due to Change in Cirrhosis or Child-Pugh Score	~~Subjects on a modified dosing regimen who~~ demonstrate a change in cirrhosis status 7.5.4 ~~and~~/or Child-Pugh Score7.5.5 should ~~have their dose of investigational product modified to match their current status per the appropriate dosing regimen (see Section ,)~~; ~~however, changes to~~ the dosing regimen ~~are not mandatory and should be based on clinical judgment as well as changes in status~~. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and ~~should not necessarily result in~~ a change to the dosing regimen. ~~Investigators may contact the Medical Monitor at any time to discuss potential changes to dosing.~~ Possible scenarios for dosing modifications include: • Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C • Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh	**When subjects** demonstrate a change in cirrhosis status (**as assessed per Section 7.5.4)** or Child-Pugh Score (**Section 7.5.5 dosing** should **be reassessed and** the dosing regimen **modified appropriately**. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters **(eg, increase in INR due to vitamin K deficiency)** should be documented appropriately and **discussed with the Medical Monitor before any continuation** or change to the dosing regimen. Possible scenarios for dosing modifications include: • Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C • Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study Subjects may titrate dose and dosing frequency up or down as appropriate, within the dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-**Month and 2**-Month Post-Titration Assessment must be	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	Score from A to B or C at any point in the study • ~~Improvement in classification of Child-Pugh Score from C to B~~ • ~~Improvement in classification of Child-Pugh Score from B to A; these subjects may be eligible to transition to the standard dosing regimen~~ Subjects may titrate dose and dosing frequency up or down as appropriate, within the ~~appropriate~~ dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.10).	performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.7).	
Appendix A, Unscheduled Titration Visit, Optional Visit	…: The ~~±~~ 1 week window ~~week~~ related to the ~~1~~ month Post-Titration Visit can be ~~extended for~~ ~~up~~ to ~~an additional~~ 5 weeks to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the ~~window~~ ~~is extended past +1 week allowed~~ visit ~~window, at a minimum, a telephone safety contact~~ should ~~then~~ be performed ~~1 month post-titration.~~	…: The ±1 week window related to the **2**-month Post-Titration Visit can be **modified** to **occur 2** weeks **earlier or 2 weeks outside of the allowed visit window** to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the 2-**month Post-Titration Visit** is **performed during a regularly scheduled study** visit, **all scheduled procedures associated with that visit** should be performed.	

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Version 6: 05 November 2019

EudraCT Number: 2014-005012-42

Sponsor

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CONFIDENTIAL

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

PPD

PPD PhD

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

05 NOV 2019
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 747-302. 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 747-302 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312 and all applicable regulatory requirements.

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

Emergency Contact Information

Medical Monitor – 24-hour Emergency Reporting

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid (OCA)

Name of Active Ingredient:

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

Title of Study:

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

Investigators and/or Study Center(s):

Approximately 170 investigational study sites, globally.

Studied Period (Years):	**Phase of Development:**
The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Phase 4: US, Canada, and the EU Phase 3b: All other regions

Objectives:

Primary

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary cholangitis (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

Secondary

- To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above.
- To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.
- To assess the effect of OCA compared to placebo on progression to cirrhosis.
- To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).
- To assess the effect of OCA compared to placebo on disease progression via the following:

- Liver biochemistry
- Markers of inflammation and fibrosis

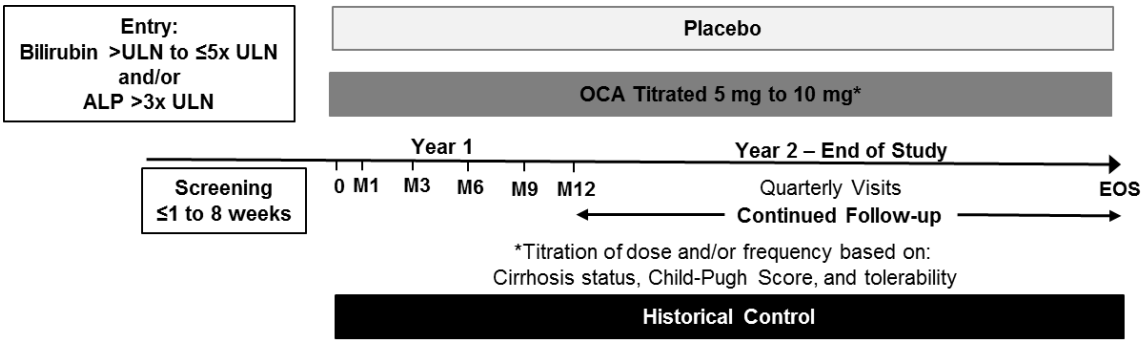
- To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.
- To characterize the pharmacokinetics (PK) of OCA and its conjugates in a subset of subjects.
- To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.
- To assess the safety and tolerability in subjects treated with OCA compared to placebo.

Methodology:

This Phase 3b/4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened twice during a 1- to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP) and total bilirubin values (refer to Section 9.7.3).

Investigational product will be taken orally, once daily for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (> upper limit of normal [ULN]/ ≤ULN). A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.

Schematic Diagram Study 747-302:



EOS = end of study; ULN = upper limit of normal

Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN). Subsequent dose titration(s) for subjects classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:

- Noncirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.
- For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.

- Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B or Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly (at least 3 days apart), based on tolerability and biochemical response.

Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Planned Dosing Regimen	
	Standard	**Modified**
	Noncirrhotic/ Child-Pugh A	**Child-Pugh B or Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly

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

With the exception of liver transplant, if a subject experiences a suspected or confirmed clinical outcomes event, the subject should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for discontinuation outlined in the protocol. Subjects who discontinue investigational product are expected to be followed through to study closure (or at the discretion of the Sponsor). Additional information regarding subject follow-up and different options available to subjects is provided in Section 7.9 and Section 8.4.

Number of Subjects (Planned):

Approximately 428 subjects are planned to be enrolled in the study. In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with American Association for the Study of Liver Diseases [AASLD] and the European Association for the Study of the Liver [EASL] practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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
2. A mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past ≥3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0
5. Contraception: Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥1 highly effective method of contraception during the study

and for 30 days after the end of treatment. Highly effective methods of contraception per the CTFG guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of contraception are as follows:

- Intrauterine device
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy (partner)
- Combined (estrogen and progestogen containing) hormonal contraception (eg, oral, intravaginal or transdermal) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
- Progestogen-only hormonal contraception (eg oral, injectable or implantable) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
- Sexual abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).

6. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
   - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
   - Cirrhosis with complications, including history (within the past 12 months) or presence of:
     - Variceal bleed
     - Uncontrolled ascites
     - Encephalopathy
     - Spontaneous bacterial peritonitis
   - Known or suspected HCC
   - Prior transjugular intrahepatic portosystemic shunt procedure

- Hepatorenal syndrome (type I or II) or Screening (Visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)

3. Mean total bilirubin >5x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions)
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
7. Known history of human immunodeficiency virus infection
8. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease or fractures within 3 months prior to Day 0)
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0
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-month 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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
14. UDCA naïve (unless contraindicated)

Investigational Product, Dosage and Mode of Administration:

OCA (5 mg or 10 mg tablets)

Reference Therapy, Dosage and Mode of Administration:

Placebo (matching tablets)

Duration of Treatment:

The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

Criteria for Evaluation:

Primary Objectives	Assessments
Clinical outcomes	• Death (all-cause) • Liver transplant • MELD score ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)

	• Uncontrolled ascites (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
Secondary Objectives	
Individual components of the primary endpoint	As listed above and including liver-related death
Progression to cirrhosis	Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (ie, Fibroscan® transient elastography [TE]) confirmed by biopsy unless not medically indicated
HCC	Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy
Change in baseline liver biochemistry	Liver biochemistry (see Table 12 for list of analytes to be tested)
Inflammation and fibrosis	IgM, C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), fibroblast growth factor-19 (FGF-19), cytokeratin-18 (CK-18), enhanced liver fibrosis (ELF), and Fibroscan® TE
Clinical outcomes compared to historical controls	Similar endpoints as used for the primary objective where available including liver transplant and death
PK	OCA and its conjugates
Health outcomes and economics research	Including the following: Cost-effectiveness and resource utilization Quality of life (Fatigue Impact Score and EQ-5D-5L)
Safety and tolerability	Including the following: Treatment-emergent adverse events including adverse events of special interest Clinical laboratory values

Statistical Methods:

Analysis Populations

The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP), Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBC Historical Control. Descriptions of subject populations are provided in Section 13.1.1.

Efficacy Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint will be the time to first occurrence of one of the following:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

All events will be adjudicated by an independent committee.

Primary Efficacy Analysis

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. The 2 treatment groups will be compared 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 its 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Key Secondary Efficacy Analyses

The key secondary efficacy endpoints are as follows:

- Time to first occurrence of MELD score ≥15
- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Additional Secondary Efficacy Analyses

The following time-to-event secondary efficacy analyses will compare OCA versus placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Progression to cirrhosis
- Time to occurrence of HCC
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls.

Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as Baseline TE where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at Baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.

For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2.

Further details on efficacy, health outcomes, and PK analyses are specified in Section 13.

Safety Analyses

Safety data, including AEs, AEs of special interest including pruritus and hepatic safety, vitals, electrocardiogram, and clinical laboratory results will be summarized by treatment group for the Safety Population.

Sample Size Justification

The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN. The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years of subject accrual and 6 years of follow-up
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.
- A dropout rate of 10% is assumed.

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

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

TABLE OF CONTENTS

List of Tables

LIST OF FIGURES

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
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
CAC	Cardiovascular Adjudication Committee
CDCA	chenodeoxycholic acid
CI	confidence interval
CK-18	cytokeratin-18
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
DILI	Drug-induced liver injury
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
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FIS	Fatigue Impact Scale
FXR	farnesoid X receptor

Abbreviation or Specialist Term	Explanation
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine 6α-ethyl chenodeoxycholic acid
HCC	hepatocellular carcinoma
HCP	health care professional
HDL	high-density lipoprotein
IB	Investigator's 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
LDL	low-density lipoprotein
LTSE	long-term safety extension
MACE	major adverse cardiovascular events
MELD	model of end stage liver disease
MRS	Mayo Risk Score
OCA	obeticholic acid (also known as INT-747)
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
PIS	patient information sheet
PK	pharmacokinetic
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SUSAR	suspected unexpected serious adverse reaction

Abbreviation or Specialist Term	Explanation
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 Primary Biliary Cholangitis and Obeticholic Acid

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 United States (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.

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), 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 (Pellicciari 2002). 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 747-302 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. Mechanism of Action of Obeticholic Acid

OCA is a 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

OCA's potent FXR agonist effects are believed to account for the predominant efficacy of the investigational product. Some of the pharmacological properties of OCA and other FXR agonists that have been elucidated in animal models of chronic liver disease relevant to the treatment of PBC include the following:

- Improvement in hepatic choleresis with reduced inflammation and necrosis
- Prevention and reversal of hepatic fibrosis

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

5.3. 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.

5.4. Clinical Experience with Obeticholic Acid

As of 26 May 2019, approximately 5386 subjects have been enrolled in the clinical development program for OCA. Approximately 3926 subjects have received at least 1 dose of OCA in completed and ongoing clinical trials.

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.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double-blind Phase 3 study (747-301). Following the double-blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301.

- Study 747-201 (59 subjects) 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 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects 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 subjects) was a Phase 3, double-blind, placebo-controlled, parallel group study followed by an LTSE using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the

proportion of subjects reaching specific criteria for ALP and bilirubin (ALP <1.67× 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 <1.67× 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 10 mg OCA 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. The LTSE phase of Study 747-301 is ongoing (a final CSR is pending); the LTSE phases of Study 747-201 and Study 747-202 are complete.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rationale for Study Design

OCA is a modified bile acid and FXR agonist that is derived from the primary human bile acid chenodeoxycholic acid. The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC.

PBC is characterized by biochemical increases in ALP and GGT enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009). Both the American Association for the Study of Liver Diseases (AASLD) (Lindor 2009) and the European Association for the Study of the Liver (EASL) (EASL 2009) guidelines base the biochemical component of PBC diagnosis on elevations of ALP. In addition, a growing literature supports the use of biochemical endpoints, specifically serum ALP alone or with other parameters such as bilirubin, to manage subjects, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Beuers 2011, Momah 2012). Data from the Global PBC Study Group (Lammers 2013), which has built a database tracking biochemical status and clinical outcomes in several thousand PBC subjects, provides evidence for the use of the composite biochemical endpoint of ALP and bilirubin as an acceptable surrogate endpoint.

Study 747-301, a Phase 3 double-blind study, evaluated the safety and efficacy of OCA at doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability) and 10 mg and used a composite biochemical endpoint of ALP and bilirubin as a surrogate endpoint. In this study, both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well-tolerated. As a result, starting subjects on 5 mg OCA and titrating to 10 mg based on tolerability and clinical response appears to be an appropriate dosing strategy in subjects with PBC.

Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate

biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study. Despite the observational evidence that links ALP and bilirubin to clinical outcomes in PBC, it is necessary to prospectively validate these surrogate endpoints. As such collecting outcome information in Study 747-302 is of the utmost importance.

5.5.2. Rationale for Dose

5.5.2.1. Rationale for OCA Dose

The safety and tolerability of multiple doses of OCA have been established in subjects with PBC at doses up to 50 mg. As demonstrated in the Phase 2 PBC studies (Studies 747-201 and 747-202), OCA significantly reduced serum ALP levels at doses of 10 mg, 25 mg, and 50 mg, but with an increase in the incidence and severity of pruritus at higher dose levels. The Phase 3 PBC study (Study 747-301) subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus. Based on these data, the approved dosing regimens for OCA for the treatment of patients with PBC are 5 mg and 10 mg.

The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose for at least 3 months, increasing to 10 mg OCA, if tolerated.

5.5.2.2. Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment

Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh Score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in Phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.

Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose (full modified dosing regimen is described in Appendix A).

5.5.2.3. Rationale for Control Groups

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 a standard of care effect. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with PBC.

Historical Control Group

The available robust historical PBC observational datasets (UK-PBC and Global PBC Study Group) will also be leveraged to provide further comparative evaluation of the clinical benefit of OCA. Each database includes >6000 patients with long-term follow-up.

Comparison of OCA treatment to the historical controls may provide utility in addressing potential bias or confounds associated with the placebo arm. For example, bias associated with the potential addition of commercial OCA and/or differences in long-term standard of care between the treatment arms including ancillary treatments and diagnostics.

Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons (ie, comparisons to historical and placebo controls will be evaluated separately).

5.6. Importance of Monitoring of Disease Progression

Given PBC is a chronic, progressive liver disease, it is important that subjects with PBC are closely monitored to ensure early identification of potential disease progression to cirrhosis, decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve subject oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring.

Subjects will be monitored for potential hepatic injury and/or decompensation and progression to cirrhosis (Section 7.5). Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures post dose-adjustment are described in Section 7.6 and Section 7.7. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.

5.7. Summary of Known Potential Risks with OCA

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, including jaundice, worsening ascites and primary biliary cholangitis flare, 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), as early as one month after starting treatment with OCA.

In addition, 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 current version of the OCA Investigator's Brochure.

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 individual subject and aggregate data from both the Phase 3 clinical outcomes study in subjects with PBC (Study 747-302) and the Phase 3 pivotal studies in subjects with NASH fibrosis (Study 747-303) and NASH cirrhosis (Study 747-304) on a quarterly basis, in an unblinded fashion, and in closed sessions (without the Sponsor's participation). In the quarterly DMC meetings to date, the DMC has recommended the studies continue without modification.

Following a request from the FDA to provide an up-to-date DMC report analyzing unblinded data on respective incidence of cholecystitis, cholelithiasis, and pancreatitis by treatment group across all ongoing clinical studies, an ad hoc DMC review was held and the DMC recommended that:

- As it concerned pancreatitis, all studies continue without changes.
- For subjects in Study 747-303, investigational product should be uninterrupted in subjects who experience symptomatic cholelithiasis and/or cholecystitis.

The Sponsor implemented the DMC recommendations across the NASH program but not the PBC program.

Post-Marketing Cases in PBC

As of 26 May 2019, the estimated cumulative patient exposure from marketing experience is 7694 patient-years.

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 current version of the OCA Investigator's Brochure for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess the effect of OCA compared to placebo, in conjunction with established local standard of care on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

6.2. Secondary Objectives

- To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above.
- To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.
- To assess the effect of OCA compared to placebo on progression to cirrhosis.
- To assess the effect of OCA compared to placebo on time to occurrence of HCC.
- To assess the effect of OCA compared to placebo on disease progression via the following:
  - Liver biochemistry
  - Markers of inflammation and fibrosis
- To assess the effect of OCA compared to historical controls on liver-related clinical outcomes.
- To characterize the PK of OCA and its conjugates in a subset of subjects.
- To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilization, and quality of life measures in subjects treated with OCA compared to placebo.
- To assess the safety and tolerability in subjects treated with OCA compared to placebo.

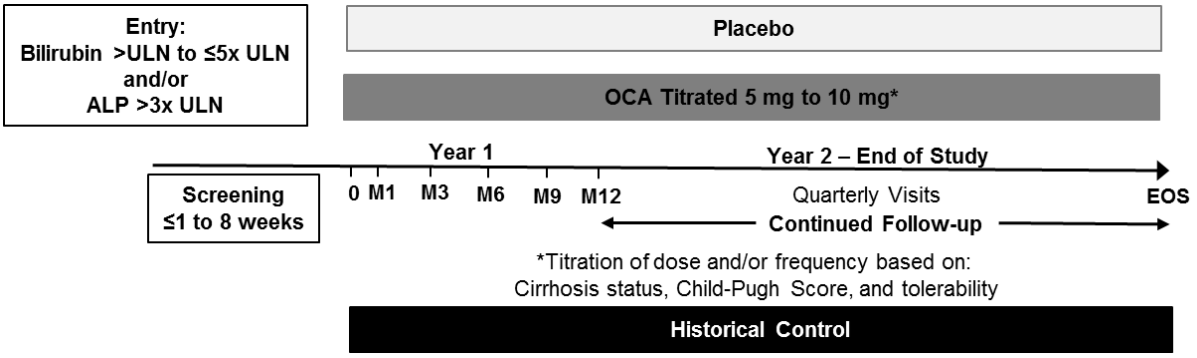
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 3b/4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened twice during a 1- to 8-week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3).

Investigational product will be taken orally, once daily for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C. The randomization will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/ ≤ULN). A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.

Figure 1: Schematic Diagram Study 747-302



EOS = end of study; ULN = upper limit of normal

Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (Up-titration should be considered when ALP and/or total bilirubin are >ULN). Subsequent dose titration(s) for subjects classified as Child Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration.

Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:

- Noncirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.
- For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.
- Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B or Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly (at least 3 days apart), based on tolerability and biochemical response.

Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Planned Dosing Regimen	
	Standard	**Modified**
	Noncirrhotic/ Child-Pugh A	**Child-Pugh B or Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly

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

With the exception of liver transplant, if a subject experiences a suspected or confirmed clinical outcomes event, the subject should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for discontinuation outlined in the protocol. Subjects who discontinue investigational product are expected to be followed through to study closure (or at the discretion of the Sponsor). Additional information regarding subject follow-up and different options available to subjects is provided in Section 7.9 and Section 8.4.

7.1.1. Schedule of Study Procedures

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2)

	Screening Visits		Day 0	M 1	M2	M 3	Post-Titration Visits[b]	M 6	M 9	M 12
	1	2[a]								
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**+1 wk**	**+1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Informed Consent	X									
Medical/PBC History[d]	X									
Cirrhosis Status Assessment[e]	X									
Inclusion/Exclusion Criteria	X	X	X							
Physical Exam	X			X	X		X	X		X[d]
Assessments for Child-Pugh Score[f]	X		X	X	X	X	X	X	X	X
Vital Signs (including weight)	X[g]		X			X		X	X	X[g]
12-Lead Electrocardiogram	X									X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X					X		X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[h]			X							X
Fibroscan® TE[i]			X					X		X
Endoscopy[j]			X							X
Hepatic Ultrasound[k]		X						X		X
Gallbladder Assessment (Ultrasound)		X[k]								
Adverse Events	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Health Outcome Assessments[l]			X			X		X	X	X

Table 1: Schedule of Study Procedures-Screening to Month 12 (Table 1 of 2) (Continued)

	Screening Visits		Day 0	M 1	M2	M 3	Post-Titration Visits[b]	M 6	M 9	M 12
	1	2[a]								
Visit Windows (+/-)[c]	**3 to 8 wk prior to Day 0**	**1 to 6 wk prior to Day 0**		**±1 wk**	**±1 wk**	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Randomization/Treatment Assigned			X							
Dose Titration: Standard Dosing[m,n]						X		X (if applicable)		
Dose Titration: Modified Dosing (if applicable)[n,o]						X		X	X	X
Dispense Investigational Product[o]			X			X		X	X	X
IP Accountability/Compliance				X	X	X	X	X	X	X
Dosing Diary			X	X	X	X	X	X	X	X
LABORATORY EVALUATIONS[p]										
Urinalysis	X		X							X
Urine-based β-hCG Pregnancy Test[q]	X		X							
Chemistry/Hematology/Coagulation[p]	X	X[a]	X	X	X	X	X	X	X	X
Amylase and Lipase			Sample to be collected if the subject experiences acute pancreatitis or cholecystitis							
Review Progression to Cirrhosis Algorithm				X	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)			X			X		X	X[r]	X
Markers of Hepatic Fibrosis and/or Inflammation[s]			X					X		X
Genetics[t]			X							X

AE = adverse event; ALP = alkaline phosphatase; β-hCG = beta human chorionic gonadotropin; eCRF = electronic case report form; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; HCC = hepatocellular carcinoma;
IP = Investigational Product; M = month, MRS = Mayo Risk Score; TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. Refer to Section 9.7.3 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility. Samples for hematology and coagulation will not be collected at Screening Visit 2.

[b] Post-Titration visits must be performed 1 month (± 1 week) and 2 months (±1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. See Appendix A for additional guidance. In subjects following the standard dosing regimen, the Post-Titration Visit must be performed 1 month (±1 week) and 2 months (±1 week) after the first up-titration to 10 mg OCA or matching placebo.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] Medical history at Screening and the yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] Presence or absence of cirrhosis should be assessed per Section 7.5.4. Cirrhosis status should be repeated as clinically indicated.

[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] Height will be collected at this visit.

[h] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.5).

[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. Please refer to Section 9.7.4 for additional information related to the allowed windows at Day 0 for this procedure.

[j] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.4 for additional information related to the allowed window at Day 0 for this specific procedure.

[k] Ultrasound will be conducted to enhance HCC surveillance and for gallbladder assessment at Screening. If ultrasound was not performed at Screening and the historic ultrasound is >3 months from Day 0, perform a hepatobiliary ultrasound at the Day 0 visit.

[l] Health Outcome Assessments: Data related to nonstudy related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[m] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[n] Dose Titration is based on cirrhosis status (Section 7.5.4) and Child-Pugh Score (Section 7.5.5). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

[o] Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

[p] The subject 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. MELD and MRS values will be calculated based on serum chemistry and coagulation values at each visit.

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

[r] Only OCA PK samples will be collected at Month 9 at select study sites in a subset of subjects. Please refer to Section 9.7.10 for the PK sampling schedule.

[s] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[t] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. If a Baseline (eg, Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2)

	Year 2 Through End of Study					
	M 3 continued follow-up	**Post-Titration Visits[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Physical Exam[d]		X			X	X
Assessments for Child-Pugh Scores[e]	X	X	X	X	X	X
Vital Signs (including weight)			X		X[f]	X[f]
12-Lead Electrocardiogram					X	X
Subject Questionnaires (5-D Pruritus Scale and Pruritus VAS)			X		X	X
Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)[g]					X	X
Fibroscan®TE[h]			X		X	X
Endoscopy[i]					X	
Hepatic Ultrasound[j]			X		X	X
Adverse Events	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X
Health Outcome Assessments[k]	X		X	X	X	X
Dose Titration (if applicable)[l]	X		X	X	X	
Dispense Investigational Product	X		X	X	X	
IP Accountability/Compliance	X	X	X	X	X	X
Dosing Diary	X	X	X	X	X	X
LABORATORY EVALUATIONS[m]						
Urinalysis					X	X
Chemistry/Hematology/Coagulation[m]	X	X	X	X	X	X
Amylase and Lipase	Sample to be collected if the subject experiences acute pancreatitis or cholecystitis					
Review Progression to Cirrhosis Algorithm	X	X	X	X	X	X
OCA, C4, and FGF-19 (plasma)[m]					X	X

Table 2: Schedule of Study Procedures-Year 2 Through End of Study (Table 2 of 2) (Continued)

	Year 2 Through End of Study					
	M 3 continued follow-up	**Post-Titration Visits[a] (if applicable)**	**M 6 continued follow-up**	**M 9 continued follow-up**	**M 12 continued follow-up**	**EOT/ EOS[b]**
Visit Windows (+/-)[c]	**±2 wk**	**±1 wk**	**±2 wk**	**±2 wk**	**±2 wk**	**±2 wk**
Markers of Hepatic Fibrosis and/or Inflammation[n]			X		X	X
Genetics[o]					X	

AE = adverse event; β-hCG = beta human chorionic gonadotropin; EOS= End of Study; EOT = End of Treatment; FGF-19 = fibroblast growth factor-19; FIS = Fatigue Impact Scale; IP = Investigational Product; M = month, MRS = Mayo Risk Score; TE = transient elastography; VAS = Visual Analogue Scale; wk = week

[a] Post-Titration Visits must be performed 1 month (±1 week) and 2 months (±1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. See Appendix A for additional guidance. In subjects following the standard dosing regimen, the Post-Titration visit must only be performed 1 month (±1 week) and 2 months (±1 week) after the first up-titration to 10 mg OCA or matching placebo.

[b] As soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Visits should be based on Day 0 (not on the prior visit) with the exception of the Post-Titration Visit, which is based on the date of titration.

[d] The yearly physical exam will include an assessment of smoking and alcohol consumption history and current habits for both.

[e] 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 case report form.

[f] The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected (See Section 11.1.2.2 and Section 12.2.5).

[g] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available.

[h] Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices.

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

[j] Health Outcome Assessments: Data related to nonstudy related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.

[k] Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.

[l] Dose Titration is based on cirrhosis status (see Section 7.5.4) and Child-Pugh Score (Section 7.5.5). The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response. Subsequent dose titration(s) for subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A.

[m] The subject should be instructed to fast overnight (at least 8 hours) prior to each visit. Fasting is required prior to all study visits, but water is permitted. MELD and MRS values will be calculated based on serum chemistry values at each visit.

[n] Markers of hepatic fibrosis and/or inflammation are defined in Section 11.1.2.

[o] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.

7.1.2. Study Duration

The study is event driven and total duration will be determined by the time required to accrue approximately 127 primary endpoint events, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.

7.2. Number of Subjects

It is expected that approximately 428 subjects will be randomized in the study to achieve 127 adjudicated primary endpoint events. In the event additional subjects are needed to complete enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

7.3. Planned Dosing Regimen

Subjects will be randomized to treatment with either OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined Section 7.5.4) and applicable Child-Pugh Score (see Section 7.5.5) as outlined in Section 7.4.

Table 3: Planned Dosing Regimen by Cirrhosis and Child Pugh Score

	Scheduled Dosing Regimen	
	Standard	**Modified**
	Noncirrhotic/ Child-Pugh A	**Child-Pugh B or Child-Pugh C**
Starting Dose [a] (Day 0)	5 mg daily	5 mg once weekly
Titration 1 [b] (≥Month 3)	10 mg daily	5 mg twice weekly[c]
Titration 2 [b] (≥6 weeks after Titration 1)	NA	10 mg twice weekly[c]

[a] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening.
[b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4).
[c] Dosing per the twice weekly schedule must be at least 3 days apart.

Non-Cirrhotic or Child-Pugh A

Subjects who are noncirrhotic or classified as Child-Pugh A at screening will receive 5 mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product and assessment of biochemical response. Up-titration should be considered when ALP and/or total bilirubin are >ULN. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the investigational product tolerability assessment before up-titration can occur (see Section 7.4.1).

For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.

Cirrhotic and Child-Pugh B or C

Subjects with cirrhosis (see Section 7.5.4) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, initiating 5 mg OCA or matching placebo once weekly. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks and meet the dose titration criteria should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

The dosing regimen should be determined as described shown in Table 13. Investigators should follow the dosing/titration schedule as shown described in Section 7.4 and Appendix A.

7.4. Dose Titration 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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 7.5.4 and Section 7.5.5) or Child-Pugh 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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3. A 1-Month and 2 Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.1 and Section 9.7.7).

Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.

Tolerability Dose Titration - Investigators may decrease the dosing frequency or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability; see Section 7.4.1).

Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 7.5.4) or Child-Pugh Score (Section 7.5.5) dosing should be reassessed and the dosing regimen modified appropriately. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change to the dosing regimen. 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, biochemical response, and clinical judgment.

Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 7.5.4. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the Investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).

Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters (eg, increase in vitamin K resulting in change in INR) should be documented appropriately and discussed with the Medical Monitor before any continuation or change to the dosing regimen (Appendix A).

Child-Pugh Scores will be calculated during screening, at each scheduled study visits, and at unscheduled visits in the event of signs or symptoms of suspected hepatic injury or decompensation are present. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 7.5.4) and/or Child-Pugh Score is observed independent of a study visit, the subject 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.

Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.

7.4.1. Pre-Titration Tolerability Assessment Requirements

Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigative product (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the Post-Titration Assessment visits (for titration prior to or at the

subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.

To be eligible for a dose up-titration:

- Subjects 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.
- There must be no clinically significant increase (as determined by the Investigator) in the subject's liver function tests.

7.5. 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). Child Pugh Scores should only be applied in patients who have evidence of cirrhosis at screening or demonstrate evidence of cirrhosis at screening or progression to cirrhosis during the study based on criteria presented in Section 7.5.4. 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 7.1.1. Based on the assessments of signs and symptoms of hepatic injury and liver biochemistry, the investigational product may be interrupted or discontinued per criteria discussed in Section 7.5.2 and Section 7.5.3, and close monitoring procedures will be implemented (Section 7.7).

7.5.1. Signs and Symptoms of Hepatic Injury or Decompensation

Subjects 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: eg, 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: eg, confusion, swelling of the legs or abdomen
- Non-specific signs and symptoms of impaired health: eg, 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 subject 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 7.5.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.5 (3) triggering of investigational product interruption or discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 12.1.5.1 and Section 12.1.5.2), and (5) contact with the Medical Monitor.

7.5.2. Liver Biochemistry Assessments for Suspected Hepatic Injury or Potential Hepatic Decompensation

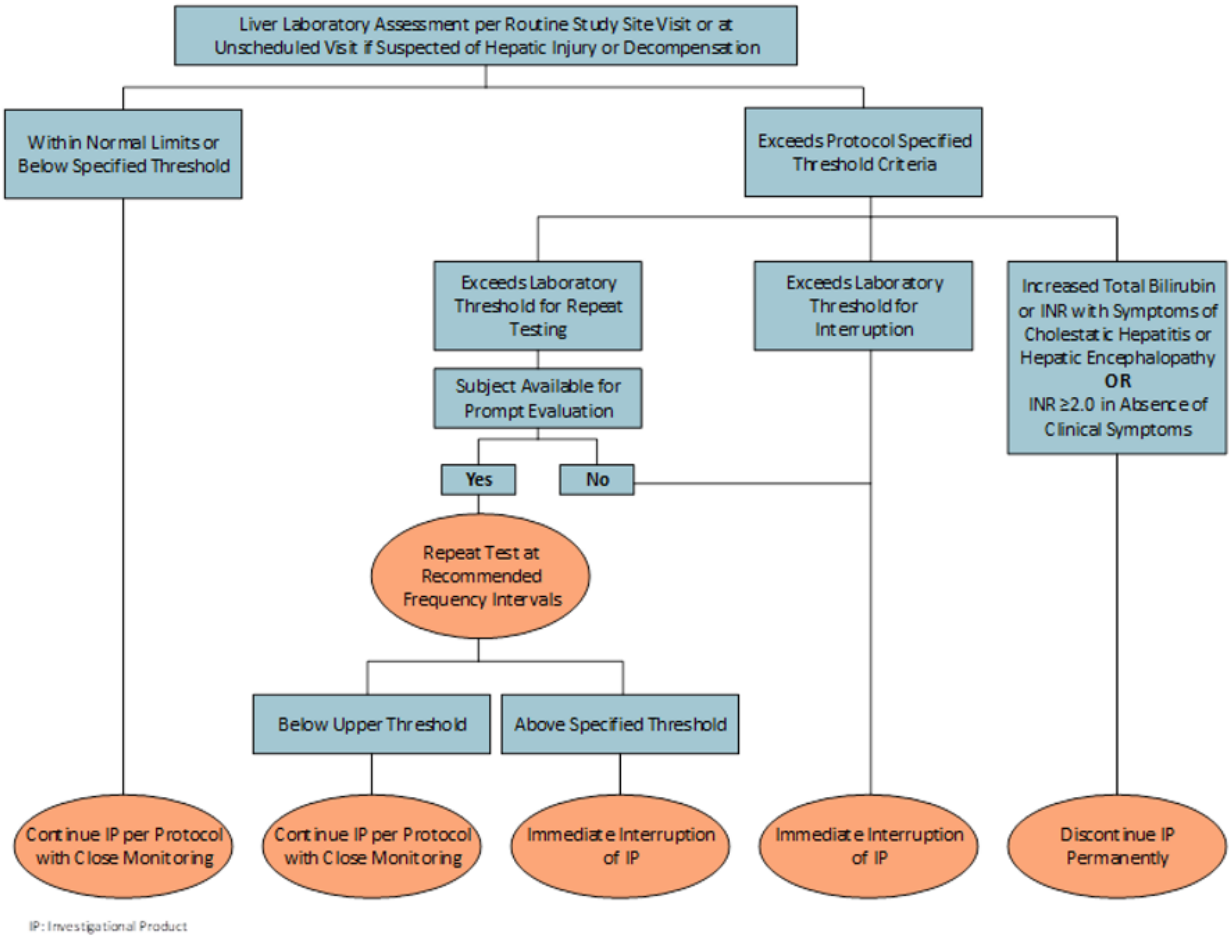
Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of subjects for potential hepatic injury or hepatic decompensation. These assessments will be performed at:

- 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 subject 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 subject evaluation (depending on the repeat result) are summarized in Table 4.

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 4: 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 subject 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 threshold	
B. 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 subject 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]		
>0.3unit increase from baseline	Closely monitor until normalization or stabilization. If values continue to increase relative to the baseline value, interrupt IP.	The subject 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 subjects 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 subjects' 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.

7.5.3. Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events

Subjects will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for the monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 5.

Investigational product should be discontinued permanently if the subject received a liver transplant or experiences multi-organ failure as defined in Table 5, Part A). Subjects should continue to return for scheduled study visits for safety follow up.

Subjects who experience other potential hepatic decompensation events defined in Table 5, Part B should be closely monitored until normalization or stabilization. Subjects may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.

Table 5: 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 4, 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.

7.5.4. Assessing Cirrhosis

7.5.4.1. Determination for Dosing Regimen

To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of determining dosing is defined as a

subject who has documented evidence or presence of one or more of the following cirrhosis indicators:

Biopsy results consistent with PBC Stage 4 (Ludwig 1978)

- TE 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)

Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A and Section 7.3).

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

7.5.4.2. Progression to Cirrhosis

When a subject identified as noncirrhotic at Baseline per the criteria listed in Section 7.5.4 exhibits any signs or symptoms associated with progression to cirrhosis, as defined by the same criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy (centrally read) unless not medically indicated. Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis.

Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.

Sites participating in the paired biopsy substudy must confirm progression to cirrhosis by biopsy as per the information outlined in protocol Addendum 2.

All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.

7.5.5. Child-Pugh Score

Child-Pugh (CP) 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 6 and can range from 5-15. Although CP score calculation will automatically be computed in all subjects, it should only be applied to subjects who meet criteria for progression to cirrhosis. Dose adjustment or discontinuation should not be considered based solely on the CP score, in subjects who do not meet criteria for presence of cirrhosis.

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). Sponsor 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 6: 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	NA	None	Mild	Moderate-Severe
Hepatic encephalopathy[a]	NA	No	Grade 1 or 2	Grade 3 or 4

INR = international normalized ratio; NA=not applicable

[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
Child-Pugh criteria: Pugh 1973, Lucey 1997, Vilstrup 2014.

7.5.5.1. Mayo Risk Score

Mayo Risk Score (MRS) (Dickson 1989) is calculated and reported within the EDC system based on data entered into the eCRF. Calculation of MRS includes Investigator assessment of peripheral edema and the use of diuretic therapy, which will be assessed during adverse event and concomitant medicine review at the scheduled visits and entered into the eCRF, as well as total bilirubin, albumin, and prothrombin time results obtained from the central laboratory data.

7.6. 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 safety and/or 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 7), investigational product should be initiated at a lower dose and subjects 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 7. 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 terminate at the time when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Table 7, and the Investigator assesses it as safe to continue. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. If a subject discontinues investigational product and cannot continue to attend regularly scheduled study visits, the subject should be strongly encouraged to participate in study follow-up via phone calls or electronic medical record review as described in Section 7.9.

Table 7: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge

DOSE ADJUSTMENT		
Criteria	**Action Taken with IP**	**Adjustment**
Progress to cirrhosis and have CP A cirrhosis (CP score <7)	Adjust to a maximum daily dose of 10 mg (or equivalent placebo) in a blinded fashion	Not applicable. Remain at maximum daily dose of 10 mg (or equivalent placebo) for remainder of study.
Progress to CP B or C cirrhosis (CP score ≥7)	Adjust IP dose to 5 mg once weekly, then titrate to a maximum 10 mg twice weekly (at least 3 days apart).	After a minimum of 3 months, if at a lower dose, subjects may titrate to a maximum IP dose of 10 mg twice weekly per Investigator discretion.
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 4)[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.

Table 7: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge (Continued)

Other liver biochemistries indicative of suspected hepatic injury are outside upper threshold criteria upon repeat testing as defined in Part A of Table 4[d]	Interrupt after confirmation by repeat testing	
Liver biochemistries indicative of potential hepatic decompensation in the absence of symptoms (see Part B of Table 4)[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 5)	Closely monitor until normalization	The subject 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	
Pregnancy	Interrupt	Patient should continue with the study visit schedule. The subject may re-start IP when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor
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)	Discontinue / No Rechallenge	Discontinue IP permanently and continue to return for scheduled study visits for safety follow up. Monitor closely for clinical outcomes per protocol. 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 4) are observed in the presence of clinical symptoms of cholestatic hepatitis or hepatic encephalopathy[f]		
Multi-Organ failure requiring hospitalization		
Liver transplantation		

Fully resolved = Return to baseline levels or return to within normal limits (WNL). IP = investigational product

[a] If subject 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 Postbaseline ≥3x baseline, Baseline >ULN and Postbaseline ≥2x Baseline, ALT or AST >3x baseline (and >ULN)

[d] ALT or AST ≥2x baseline, albumin <3.2 g/L or electrolytes (sodium <130 mEq/L).

[e] Conjugated bilirubin >0.5 mg/dL increase from baseline; 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 conjugated bilirubin 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.
[g] Multi organ failure including hepatorenal syndrome Type 1 or Type 2 and acute kidney injury, hepatopulmonary syndrome, or portopulmonary syndrome.

7.7. Close Observation

If investigational product is interrupted or discontinued as described in Section 7.6, subjects 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 subject 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 subject 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 subject 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 7.5.1, Section 7.5.2, and Section 7.5.3. These cases need to be discussed with the Sponsor's medical monitor:

- Repeating liver enzyme and serum bilirubin tests as described in Section 7.5.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject 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 subject 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 (HEV) when assessing for hepatic decompensation as infection with HEV 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

7.8. Criteria for Study Termination

The Sponsor 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 DMC, it may be necessary to stop the study before all events have been accrued, and when subjects are still active on the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, poorly performing sites, as determined by the number of subjects 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 subjects for the End of Study Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 127 adjudicated events will have been accrued.

7.9. Subject Retention

The primary objectives for the end of study analysis are to evaluate the effects of OCA compared with placebo on all-cause mortality and liver-related clinical outcomes. The overall study duration is event driven and will be determined by the time required to observe the prespecified adjudicated events for the clinical outcomes' composite endpoint (Section 7.1). Therefore, it is critical that subjects continue to participate for the duration of the study to enable assessment of clinical outcomes and confirmation of the clinical benefit of OCA in PBC.

Subjects may discontinue investigational product during the study; however, these subjects are expected to continue in the study until study termination and every effort will be made by the investigator to discuss subjects' continuation in the study. Even if a subject is no longer receiving investigational product, if the subject is attending study visits or participating in study follow-up, their information will contribute to the study primary endpoint and the evaluation of clinical benefit of OCA. All information collected in the study during regular study visits and through subjects participating in follow-up will contribute to the evaluation of safety of OCA and the scientific and medical understanding PBC.

Investigators should emphasize to subjects the importance of their continuation in the study even after withdrawal of investigational product and discuss with subjects the various options for continued participation in the study:

- Continuing to attend regularly scheduled visits, or
- Allowing semi-annual telephone visits by the Investigator, or

- Allowing the Investigator to have continued access to the subjects' medical records to assess suspected major adverse cardiovascular events (MACE) and liver-related clinical outcomes

Subjects will be asked to provide both personal and primary physician(s) contact information who can provide information to the Investigator about the clinical/medical status on the subjects' behalf.

Should subjects choose to discontinue treatment or withdraw consent and fully leave the study, it will be made clear to them that they may return to their randomized treatment group should they so choose.

Additional information is described in Section 8.4.

Given the importance of subject retention, clinical site personnel should refer to specific strategies and procedures as described in a separate Subject Retention Plan that will provide additional information to facilitate subject retention.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 170 international study sites with experience in treating patients with PBC. Prospective subjects 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. Subject Inclusion Criteria

1. Definite or probable PBC diagnosis (consistent with AASLD and EASL practice guidelines; Lindor 2009; EASL 2009), as demonstrated by the presence of ≥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 in 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.
2. A mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN
3. Age ≥18 years
4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0.
5. Contraception: Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥1 highly effective method

of contraception during the study and for 30 days after the end of treatment. Highly effective methods of contraception per the CTFG guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of contraception are as follows:

- Intrauterine device
  - Intrauterine device (IUD)

    Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy (partner)
- Combined (estrogen and progestogen containing) hormonal contraception (eg, oral, intravaginal or transdermal) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
- Progestogen-only hormonal contraception (eg oral, injectable or implantable) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
- Sexual abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).

6. Must provide written informed consent and agree to comply with the study protocol

8.3. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including:
   - Hepatitis C virus infection
   - Active hepatitis B infection; however, subjects 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
   - Nonalcoholic steatohepatitis
   - Gilbert's Syndrome
2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

- History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria.
- Cirrhosis with complications, including history (within the past 12 months) or presence of:
  - Variceal bleed
  - Uncontrolled ascites
  - Encephalopathy
  - Spontaneous bacterial peritonitis
- Known or suspected hepatocellular carcinoma
- Prior transjugular intrahepatic portosystemic shunt procedure
- Hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L)

3. Mean total bilirubin >5x ULN
4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures.
5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions).
6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test by the central laboratory), or lactating.
7. Known history of human immunodeficiency virus infection.
8. Medical conditions that may cause non-hepatic increases in ALP (eg, Paget's disease or fractures within 3 months).
9. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study.
10. History of alcohol abuse or other substance abuse within 1 year prior to Day 0.
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. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
14. UDCA naïve (unless contraindicated)

8.4. Subject Withdrawal Criteria

Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. See Section 7.6 for withdrawal criteria related to potential hepatic injury and/or decompensation including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.1. The specific reason(s) for discontinuation from investigational product and/or withdrawal of consent should be recorded on the appropriate CRF.

8.4.1. Other Reasons for Discontinuation of Study or Investigational Product

In general, the site should counsel the subject on the importance of maintaining the regular visit schedule and remaining on investigational product. Subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Specific strategies to encourage continued subject participation in the study will be outlined in a Subject Retention Plan. Subjects who discontinue investigational product, but agree to follow up either through phone calls or review of electronic medical records are expected to continue to provide information regarding clinical outcomes or new interventions for PBC (such as initiating commercial OCALIVA). Early termination procedures should only be conducted if the subject withdraws consent (see Section 9.7.15).

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

- Subject begins treatment with commercially available OCALIVA.
  - If a subject begins treatment with commercially available OCALIVA, they must interrupt IP immediately and this must be reported in the treatment discontinuation eCRF to prevent double dosing and for notification of the sponsor and medical monitor.
- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- 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 subject discontinues both investigational product and study visits and procedures).

- Consent may be modified to discontinue study visits, but allow semi-annual telephone contact of subject, subject's primary care physician, or personal contacts who can provide information on behalf of the subject by the Investigator
- Consent may be modified to discontinue study visits or semi-annual telephone contact, but may allow for continued access to medical records to assess for suspected MACE, liver-related clinical outcomes, and new interventions and medications for treatment of PBC.
- Other subject follow-up options to collect study outcomes should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.

Early termination procedures should be conducted if the subject withdraws consent (see Section 9.7.15).

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

8.4.2. Withdrawal of Consent

If the subject 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 subjects volunteer for the study and that they may withdraw their consent to continue in the study at any time.

Diligent efforts must be made to determine the reason(s) for subject discontinuation (such as initiation of commercial OCALIVA or underlying adverse events). This information and date must be recorded in the appropriate case report form (CRF).

8.4.3. Requirements to Re-Initiate Investigational Product or Re-Enter the Study

Subjects who wish to re-initiate investigational product while participating in study follow-up or re-enter the study after having withdrawn consent more than 3 months since the last visit must confirm that they have not received any investigational product that is being evaluated for the treatment of PBC within 30 days or commercial OCALIVA for 3 months before restarting investigational product or within 5 half-lives of the compound (whichever was longer). Subjects are to be re-consented and new baseline visit procedures must be performed.

8.4.4. Lost to Follow-up

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

Diligent efforts to determine the reason(s) why a subject failed to return for a study visit or is lost to follow-up must be made. If the subject has provided consent, the subject's primary care physician or personal contacts who can provide information on behalf of the subject by the Investigator, must be contacted if the subject consistently fails to return for study visits. This information and date of contact must be recorded in the appropriate CRF.

8.4.5. Subject Discontinuation Notification

The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), diligent efforts should be made to contact the subject in order to determine why the subject failed to return (see Section 8.4.3). This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.15, Early Discontinuation and/or Early Termination Procedures).

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

The term investigational product refers to either OCA (provided as part of this clinical study) or matching 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 5 mg OCA tablet or one 10 mg OCA tablet, or matching placebo).

Investigational product will be taken orally, up to once daily, for the duration of the study.

All subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.1) 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 CRF, as well as any dose or dose regimen changes that occur during the study. Concomitant medications should be stable prior to Day 0.

Drug Interactions

Subjects 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 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 Investigator's Brochure (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 with OCA that may be observed in study subjects.

PBC-Specific Therapy

In general, 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 subjects' 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, subjects 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, subjects should be reminded to keep taking their blinded investigational product.

9.2.1. 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. Subjects who initiate commercial OCA therapy must discontinue investigative product and are expected to continue through the end of the study (see Section 9.7.15). The study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (see Section 9.7.15).

9.3. Treatment Compliance

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

Subjects should be instructed to complete a dosing diary to help monitor compliance to the prescribed dosing regimen. Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the subsequent visit. The Investigator or designee should perform investigational product accountability and, if applicable,

follow up with the subject to retrieve any investigational product bottles that have not been returned.

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

9.4. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Allocation to one of two treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and mean baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory. The randomization will be based on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 0. The IWRS will also serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned (refer to Section 9.5.2 below) and investigational product dispensing information (ie, bottle number[s]) will be provided.

9.4.1. Unblinding Procedures – Emergency Unblinding Procedures

Treatment assignment for individual subjects 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 subject). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the subject'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 subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial 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 subjects. Refer to Section 13.3 for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded subject data reviews in the closed session DMC minutes, which will be made available to the Sponsor only after the database is locked and the trial 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 Subject 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 subject data and to identify the site and or Investigator within study documents. This number will be recorded in the CRF.

9.5.2. Subject Numbers

Subjects 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 trial is prohibited.

9.7. Visit Procedures

9.7.1. Visit Windows

Visits should be based on Day 0 (not on the prior visit), eg, Month 3 should ideally occur 3 calendar months (± 2 weeks) following Day 0.

The visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Screening Visit 1 interval is 3 to 8 weeks prior to Day 0. Screening Visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window. See Section 9.7.3 for scenario specific visit windows that may be applicable at Screening.
Day 0	This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)
Month 1	±1 week (7 days)
Titration Visit – Standard Dosing Regimen	≥Month 3
Titration Visit 1 – Modified Dosing Regimen	≥Month 3
Titration Visit 2 – Modified Dosing Regimen	≥6 weeks after Titration Visit 1

Visit or Procedure	Visit Window and/or Interval
Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY)	≥6 weeks after Titration Visit 2
Post-Titration Visit	1 month and 2 months (±1 week [7 days]) from date of titration
Month 3 to Month 12	±2 weeks (14 days)
Quarterly visits (Months 15 to EOS)	±2 weeks (14 days)
EOT (When subject discontinues investigational product)	As soon as possible upon study discontinuation and as near as possible to last dose taken
EOS (When subject terminates the study)	The final study visit; EOS will occur concurrent with EOT if a subject discontinues investigative product at the time the subject's participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues investigative product but continues in the study.
IP Re-Initiation/ Study Re-Entry (When a subject has previously discontinued treatment/ withdrawn consent and has chosen to return to study participation)	Day 0 procedures should be conducted and the visit window will be relative to Day 0 from the original study entry.

EOS = end of study; EOT = end of treatment; IP=investigational product

9.7.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of / study to the subject and will provide his/her with a copy of the written information and informed consent form (ICF). The subject will be given sufficient time to consider the study before deciding whether or not to participate. The subject 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 s/he can withdraw from the study at any time. The subject must be willing and able to provide written informed consent before entering the study. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject. The subject will be given a copy of the written information and his/her signed and dated consent form.

Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subject will be given a signed and dated copy of the consent document.

9.7.3. Screening Procedures (1 to 8 Weeks prior to Day 0)

Two Screening Visit assessments must be performed 1 week to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Screening Visit 1 will occur 3 weeks to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 week to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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.

Collection of 2 serum chemistry samples (collected at least 2 weeks apart) during Screening is required for confirmation of the pretreatment serum chemistry values, including ALP and total bilirubin used to determine eligibility:

- All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart.
- When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.
- The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤5x ULN and/or an ALP >3x ULN).

Screening Visit 1 procedures are as follows:

- The subject is to review and sign the ICF. Informed consent must be obtained from the subject 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
- Assess for the presence/absence of cirrhosis.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment-emergent AEs.
- Record prior (if within 30 days of Screening) and current concomitant medications.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

Screening Visit 2 procedures are as follows:

- Verify inclusion and exclusion criteria for eligibility.
- Perform an ultrasound for HCC surveillance and gallbladder assessment (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within 3 months of the planned Day 0 visit, and a report/adequate data are available, a pretreatment ultrasound is not required. If the ultrasound cannot be performed at Screening Visit 2 (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 must be reviewed to assess possible exclusion criteria prior to randomization.
- Assess and record any pretreatment-emergent AEs.
- Review and record prior and concomitant medications.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry tests.
- The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.

It is acceptable to repeat laboratory evaluations or other assessments or procedures within the Screening period (Weeks -8 to -1), as appropriate. In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.

9.7.4. Day 0 Procedures (Randomization)

- Review inclusion and exclusion criteria for eligibility.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to Fibroscan® TE device. If TE has been done within 3 months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. If the TE cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, TE data is needed to inform cirrhosis assessment, etc), the procedure may be completed within the screening visit window, at Screening Visit 1 (if data is needed for cirrhosis assessment) or as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.

- Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where the device is available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed.
  - Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are $<150 \times 10^9$ /L.
- Assess and record any pretreatment-emergent AEs.
- Review and record prior concomitant medications.
- Review and record any nonstudy 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 subject only if s/he meets all inclusion criteria and no exclusion criteria.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Perform a urine-based β-hCG pregnancy test in females of childbearing potential.
- If hepatobiliary ultrasound for HCC screening and gallbladder assessment was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and fibroblast growth factor-19 (FGF-19)
  - Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF])
  - Genetics (see Section 11.1.2.3)
- Perform assessments for calculation of Child-Pugh Score.
- Access the IWRS and dispense investigational product.

- Instruct the subject to begin dosing on the day after the Day 0 visit (ie, on Day 1). Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.5. Months 1, 2 Procedures

- Perform a physical examination.
- Assess and record AEs
- Review and record prior and concomitant medications.
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 and Month 2 visit laboratory requirements:
  - At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Month 1 and Month 2 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern. The subject must also be

contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;

- A physical examination should be performed at the Month 3 visit if an onsite Month 1 or Month 2 visit was not performed.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Post-Titration Visit Procedures

- Perform a physical examination.
- Assess and record AEs.
- Review and record prior and concomitant medications
- Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm
- Provide the subject with a dosing diary to document his or her dosing.
- In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration laboratory requirements:
  - At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration Visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;
  - If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern. The subject must also be contacted via telephone at the Post-Titration Visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;
  - A physical examination should be performed at the next scheduled visit if an onsite Post-Titration Visit was not performed

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 6 Procedures

- Perform a physical examination.
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Subject questionnaires (see Section 12.2.5)
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19

  - Markers of hepatic fibrosis and/or inflammation (including ELF)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.
- For subjects who will participate in the PK assessment and are taking BAS or aluminum hydroxide- or smectite-containing antacids, they should be instructed to not take their regular dose on the morning of the study visit.

9.7.9. Month 9 Procedures

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits, but water is permitted.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- PK assessment in participating subjects at select study sites (see Section 9.7.10).
- Provide the subject with a dosing diary to document his or her dosing.

- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment

At selected investigational sites, subjects will have the option to consent to participate in an additional OCA PK assessment. PK samples will be used to support further analysis of OCA exposure-response in subjects with PBC. This is optional and subjects may decline to participate without affecting their involvement in the rest of the study. Consent to participate in the assessment can be given at any point during study participation prior to the Month 9 visit.

Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule.

Following collection of the Month 9 fasted samples (refer to Section 9.7.9, subjects who are participating in the PK assessment will each receive a single dose of investigational product (blinded OCA or placebo tablet) with approximately 240 mL of water. Subjects taking BAS or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigative product and UDCA, ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigative product (and UDCA).

Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. Samples should be collected within a window of ±5 minutes of the scheduled sample time. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4-hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink with no other food allowed until after the final 6-hour post-dose sample is collected. Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.

9.7.11. Month 12 Procedures

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessments for calculation of Child-Pugh Score
- Review progression to cirrhosis algorithm
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead electrocardiogram (ECG).

- Quality of Life and Subject questionnaires and (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an endoscopy (at all study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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. Month 3 and Month 9 Continued Follow-Up Procedures (±2 weeks)

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm
- Assess and record AEs.
- Review and record prior and concomitant medications.
- Review and record any nonstudy 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, and review dosing diary with the subject.
- Assess for dose titration, if eligible (refer to Section 7.4).
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.13. Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])

- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm
- Assess and record vital signs (weight, temperature, sitting heart rate, respiratory rate and sitting blood pressure).
- Subject questionnaires (see Section 12.2.5)

- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications
- Review and record any nonstudy 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - Markers of hepatic fibrosis and/or inflammation (including ELF).
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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

9.7.14. Month 12 Continued Follow-up Procedures (Annually [±2 weeks])

- Perform a physical examination (including smoking and alcohol consumption habits).
- Perform assessments for calculation of Child-Pugh Score.
- Review progression to cirrhosis algorithm.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).

- Perform a standard 12-lead electrocardiogram (ECG).
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to the Fibroscan® TE device.
- Perform an endoscopy (at all study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).
- Assess and record AEs.
- Review and record prior and concomitant medications
- Review and record any nonstudy 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 (refer to Section 7.4).
- Assess investigational product compliance, perform accountability, and review dosing diary with the subject.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.
- Obtain urine sample for urinalysis.
- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)
  - Genetics (see Section 11.1.2.3)
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

9.7.15. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects who discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Even if a subject is no longer receiving investigational product, if the subject is attending study visits or participating in study follow-up (through telephone visits or electronic medical record review), their information will contribute to the study primary endpoint and the evaluation of clinical benefit of OCA. All information collected in the study during regular study visits and through subjects participating in follow-up will contribute to the evaluation of safety of OCA and the scientific and medical understanding of PBC.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product, but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 8) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination (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 subject 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 and EOS procedures in the CRF.

Table 8: Early Discontinuation Scenarios

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Early Termination[b]	Discontinued	Withdrawn	No additional visits except EOT/EOS	Combined Visit, Completed as close as possible to last dose IP	
Treatment Discontinuation[b,c]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[d]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[d]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
	Investigational Product	**Consent**	**Study Visit Status**	**EOT Visit[a]**	**EOS Visit[a]**
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

[a] Refer to Section 7.1.1 Schedule of Study Procedures, Table 2 for all procedures and evaluations required at the End of Treatment and End of Study Visits.

[b] Subjects may choose to re-consent, re-enter the study, and re-initiate IP at a later date. Day 0 procedures will be repeated and the subject will resume in the visit window relative to the original Day 0.

[c] Includes initiation of commercially available OCA.

[d] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. Additional data such as information on concurrent medical conditions, co-morbidities, relevant adverse events, and concomitant medications may be collected to help facilitate adjudication of these post-study events.

Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

Prior to the EOT/EOS Visit:

If possible to do before the visit, when scheduling the EOT/EOS visit, reiterate dosing instructions and advise the subject:

- If applicable, NOT to take investigational product on the morning of the next visit, and
- To bring the investigational product bottle(s); if applicable, s/he will dose at the clinic, 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.

During the EOT/EOS Visit:

- Perform a physical examination (including smoking and alcohol consumption habits).
- Review progression to cirrhosis algorithm
- Perform assessments for calculation of Child-Pugh Score.
- Assess and record vital signs (height, weight, temperature, sitting heart rate, respiratory rate, and sitting blood pressure).
- Perform a standard 12-lead ECG.
- Quality of Life and Subject questionnaires (see Section 11.1.2.2 and Section 12.2.5).
- Perform TE at all study sites with access to the Fibroscan® TE device (not required at EOT/EOS if done within 6 months).
- Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months.
- Assess and record AEs; all ongoing "related" AEs must be followed until stable or resolved.
- Review and record concomitant medications.
- Review and record any nonstudy 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 accountability, and review dosing diary with the subject; retrieve used bottles, accordingly, and document returns.
- Verify that the subject has fasted for at least 8 hours.
  - Record fasting status in the source and CRF.
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.
- Obtain urine sample for urinalysis.

- Obtain blood samples for serum chemistry, hematology, and coagulation tests.
- Obtain blood samples for:
  - OCA, C4, and FGF-19
  - Markers of hepatic fibrosis and/or inflammation (including ELF)

For subjects who prematurely terminate investigational product and/or the study, procedures outlined in Section 8.4.1 should be followed.

Subjects who wish to re-initiate investigational product while participating in study follow-up or re-enter the study after having withdrawn consent or having discontinued treatment more than 3 months since the last visit must confirm that they have not received any investigational product being evaluated for the treatment of PBC within 30 days or commercial OCALIVA for three months before restarting investigational product or within 5 half-lives of the compound (whichever was longer). Subjects are to be re-consented and new Day 0 visit procedures must be performed. The subject will resume the study in the visit window relative to their original Day 0 visit.

9.7.16. 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.

In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin is observed during the course of the study, refer to Section 7.5 to confirm whether an unscheduled safety visit is required.

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 5 mg or 10 mg OCA 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 subject at each visit to provide enough tablets for daily 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 trial sites in support of clinical study 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 Preparation

The investigational product will be provided to the distribution center in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects before shipping to the sites.

10.5. Investigational Product Administration

Refer to Section 9.1.

10.6. 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 subject 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.

11. ASSESSMENT OF EFFICACY

11.1. Assessment of Efficacy

11.1.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant
- Model of end stage liver disease (MELD) score ≥15
- 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 or greater)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

11.1.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- Individual components of the primary endpoint
- Liver-related death
- Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.
  - Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in Addendum 2).
- HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.
- Liver biochemistry (see Table 12 for list of analytes to be tested)
- Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ELF, and Fibroscan (and others as determined during the course of the study).
- Clinical outcomes, including individual component of the primary endpoint (where available), liver transplant, and death will be compared to historical controls.
- PK of OCA and its conjugates.

- Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually. Resource utilization information will be collected from the Medical and Surgical Treatment Procedures and Office Visit Log or other CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.
- Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices.

11.1.2.1. Noninvasive Assessments of Liver Fibrosis

- Blood samples for measurement of ELF test and other analytes will be collected. The ELF test assesses: hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-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.

11.1.2.2. Other Secondary Assessments

- OCA (OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide) and C4 will be assayed to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified.
- Quality of Life questionnaires. 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 (VAS). 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 respondent's self-rate 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).
  - Fatigue Impact Scale (FIS): The FIS is a validated 40 question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has

5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994).

11.1.2.3. Other Exploratory Evaluations

- A genetics study for single-nucleotide polymorphisms (SNPs) that may be involved in PBC will be conducted for subjects and at study sites willing to provide samples at Day 0, Month 12, and every other year at the yearly visits thereafter. RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the study. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.

11.1.2.4. Potential Clinical Outcome Events

The events listed in Section 12.1.6 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 13.4) 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 suspected unexpected serious adverse reaction (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 13.4.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definitions of Adverse Events

12.1.1.1. Adverse Event

An AE is 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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE.

Subjects should be questioned in a general way, without leading the subject 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.

Subjects 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 whites of eyes, and bruising easily.

12.1.1.2. 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-subject 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 subject 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.

12.1.1.3. Treatment-Emergent Adverse Event

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

12.1.1.4. Adverse Events of Special Interest

The following decompensation events are adverse events of special interest. A subset of these events are also individual components of the primary endpoint (Section 11.1.1).

- 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, 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

12.1.1.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is defined as a suspected adverse reaction which is assessed as serious, causally related to the investigational product, and unexpected per the reference safety information (RSI) in the Investigator's Brochure.

SUSARs are subject to expedited reporting. The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening are recorded and reported as soon as possible to the relevant competent authorities (either directly or through the Eudravigilance Clinical Trials Module, as applicable), and to the Ethics Committees, no later than 7 days after knowledge by the Sponsor of such a case. Relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned (either directly or through the Eudravigilance Clinical Trials Module) and to the Ethics Committees concerned, within a maximum of 15 days of first knowledge by the sponsor. Each competent authority shall ensure that all SUSARs to an investigational product

which are brought to its attention are recorded. The Sponsor shall also inform all participating Investigators, as applicable to the local regulations.

12.1.2. 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/serious adverse event (SAE) and the investigational product is determined to be "possible" or "probable" 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 subject'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	A reaction 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 subject's clinical state.
Not Related	Any event that does not meet the above criteria.

12.1.3. Relationship of Adverse Events to Liver Biopsy

The Investigator will document her/his opinion of the relationship of an AE to liver biopsy using the criteria outlined in Table 10.

Table 10: Relationship of Adverse Events to Liver Biopsy

Relationship	Description
Related	A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.
Not Related	Any event that does not meet the above criteria.

12.1.4. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 11, must be entered on the AE CRF. 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 11: Severity of Adverse Events

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

12.1.5. Reporting of Adverse Events and Serious Adverse Events

12.1.5.1. Reporting of Adverse Events

AE data will be collected from the time that signed informed consent is obtained until the subject 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 subject'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.

In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any subject.

12.1.5.2. 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 be reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521

If an SAE is reported by email 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:

- Subject 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 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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

The Investigator is responsible for submitting information on 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, 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 12.1.6.

12.1.6. Suspected Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition qualify as SAEs (see Section 12.1.1.2). The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.5.2). 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.

Given that the liver-related clinical outcome events may also meet the criteria of a SUSAR, but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data approximately quarterly, the Sponsor will not expeditiously report suspected liver-related 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 "study event" on the AE CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.

The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 or oesophageal varices haemorrhage), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological or clinical progression to cirrhosis (preferred term: hepatic cirrhosis).

12.1.7. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF 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 subject's AE CRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Medical Monitor, 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 subject 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.

12.1.8. 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 12.1.5.2.

SAEs that occur in subjects 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 12.1.5.2.

12.1.9. Notification of Poststudy 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 12.1.5.2.

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 12.1.5.2.

12.1.10. 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 subject 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 subject 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.

Drug-Induced Liver Injury or Disease Progression

All subjects 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 from drug-induced liver injury follow-up 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

At the time of consent for new subjects (or re-consent to the protocol amendments for ongoing subjects), subjects will 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. Subjects will 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 will be instructed to promptly bring subjects 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 will 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.

12.1.11. 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 7.6 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 sae@interceptpharma.com or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

The subject 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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 12.1.5 must also be followed.

12.2. Other Safety Parameters

12.2.1. Medical History/Demographics

A complete medical history and PBC disease-specific history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, gender, race, and ethnicity) will be recorded.

12.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Section 7.1.1). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE CRF page for findings that appear after consent, and on the medical history CRF for any finding present prior to consent. Information about smoking and alcohol consumption habits will be collected at the same (follow-up) timepoints as the physical exam.

12.2.3. Vital Signs

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

12.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the Screening Visit 1, Month 12, and at EOT/EOS. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF page.

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 subject's initials, Subject ID number, date, and time.

12.2.5. Subject Questionnaires

Information about the subject's PBC disease history (ie, date of diagnosis, treatment history, pruritus history, signs and symptoms, and including smoking history) will be collected during Screening. At subsequent study visits (see Section 7.1.1), subjects will be asked to complete the following questionnaires; they may be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's study records. These may require transcription to the CRF by study site staff.

- 5-D Pruritus Questionnaire: This is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution (Elman 2010).
- Pruritus VAS: A Visual Analogue Scale (VAS) will also be used to assess pruritus in individual subjects.

12.2.6. Laboratory Assessments

Subjects will be instructed to attend any study or unscheduled laboratory visits (except Screening) in a fasted state, and subjects should remain fasted until their blood samples have been collected. At each visit, the Investigator or designee will verify that the subject has fasted for at least 8 hours and record fasting status in the source and CRF. If the subject reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits.

Blood samples for serum chemistry and hematology will be collected at every visit as detailed in the Schedule of Study Procedures (Section 7.1.1). 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 by the central clinical laboratory in a study specific laboratory 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 subjects 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 12, and the normal reference ranges for liver biochemistries are shown in Appendix C.

Table 12: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
Serum Chemistry	Albumin, blood urea nitrogen (BUN), 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 very low-density lipoprotein [VLDL] fractions and triglycerides[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	Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatine, leucocytes, nitrates, albumin/creatine ratio (if positive)
Markers of Cholecystitis and Pancreatitis	amylase and lipase
Biomarkers of Hepatic Fibrosis and/or Inflammation	IgM, C-reactive protein (CRP), TNF-α, FGF-19, CK-18, ELF, and others as determined during course of study
Genetics	DNA including single-nucleotide polymorphisms (SNPs) that may be involved in PBC; RNA
Other	OCA (parent and conjugates [glyco and tauro], OCA-glucuronide) and C4

The Investigator should manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual subject's total cardiovascular risk profile.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. 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 subject will be followed, as outlined in Section 12.1.11 through pregnancy outcome.

MELD scores and Child-Pugh score will be calculated at screening, and at all visits based on serum chemistry and coagulation.

13. STATISTICAL METHODS

A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the first interim analysis, propensity score determination, and unblinding of the double-blind subject treatment assignments.

13.1. Efficacy Analysis

13.1.1. Analysis Populations

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

- The Intent-to-Treat (ITT) Population will include all randomized subjects who receive any amount of investigational product (OCA or placebo). The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all subjects who received any amount of investigational product (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.
- The PK Population will include all OCA subjects who have at least one confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours prior to the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK population will be used for OCA PK analyses.
- The Overall Historical Control Population will include subjects from the United Kingdom (UK) -PBC Group and Global PBC Study Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.
- The UK-PBC Historical Control Population will include subjects from the UK-PBC Group databases with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

- The Global PBC Historical Control Population will include subjects from the Global PBC Study Group database with demonstrated comparability to randomized subjects in this clinical study (747-302) with respect to both subject characteristics and disease progression.

13.1.1.1. Comparability of Historical Controls

Utilization of both historical control/observational databases (UK-PBC and Global PBC Study Group), with more than 6000 subjects each, allow for a rigorous subject level meta-analysis. The historical databases include long-term follow up, detailed subject-level information such as baseline clinical characteristics, longitudinal liver biochemistry, and long-term outcomes, and span a broad range of subject characteristics that may influence disease (disease state, age, gender, and regional differences in standard of care). Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8.

13.1.2. Determination of Sample Size

The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3× ULN. The following assumptions were used in sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a hazard ratio of 0.60, and total study duration of 10 years (from first subject enrolled), allowing for 4 years of subject accrual and 6 years of follow up.
- Subjects will be randomized in a 1:1 ratio to placebo or OCA.
- The 2 groups will be compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.
- A dropout rate of 10% is assumed

Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it is estimated that approximately 428 subjects will be enrolled to attain 127 events.

13.1.2.1. Sample Size Monitoring

Conducting a long-term outcomes study given the low disease prevalence, relatively slow disease progression, and ethical considerations, which in combination will impact recruitment

and event rates, is inherently difficult. As stated in ICH E9, in long-term trials there is an opportunity to check the assumptions that underlay the original design and sample size calculations. The power stated above depends on the total number of events. Thus, the overall survival function can be estimated without unblinding.

Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated quarterly in a blinded manner. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups. Specifically, the pooled number of events will be available during the study in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional subjects may be enrolled as appropriate.

13.1.3. Primary Efficacy Analysis

The primary efficacy endpoint will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- Liver transplant
- MELD score ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month).

The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. Only adjudicated events will be included in analyses. The 2 treatment groups will be compared 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.

13.1.4. Key Secondary Efficacy Analyses

The key secondary efficacy endpoints will compare OCA to placebo on the following:

- Time to first occurrence of MELD score ≥15

- Time to liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints. Only adjudicated events will be included in time-to-event analyses. The comparison (hypothesis testing) will be conducted as specified in Section 13.1.10 in a sequential closed testing gate-keeping procedure, provided that the primary efficacy endpoint comparison is statistically significant in favor of the OCA treatment group. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

The 2 treatment groups will be compared using the same methodology as specified for the primary efficacy analysis (Section 13.1.3). The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.

Analyses of change from Baseline to end of study in ALP and total bilirubin will be compared between treatment groups using analysis of covariance (ANCOVA) with change from Baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and the Baseline values as a covariate. The same analysis will be carried out using percentage change from Baseline as the dependent variable.

Descriptive statistics of the laboratory values will be summarized by treatment group. The results, change from Baseline, and percentage change from Baseline values, as well as estimates of least-square means, standard errors, and 95% CIs, will be presented by treatment group. Estimates of the mean difference between treatment groups, the standard error of the difference, and 95% CI of the difference will be presented.

13.1.5. Additional Secondary Efficacy Analyses

The following time-to-event secondary efficacy analyses will compare OCA versus placebo using the ITT population:

- Time to each component of the primary efficacy endpoint (except MELD score ≥15 which is captured above)
- Time to development of varix/varices
- Progression to cirrhosis
- Time to occurrence of HCC
- Time to liver-related death
- Time to liver-related death or liver transplant
- Time to liver-related death, liver transplant, or MELD score ≥15

The same analysis methodology as used for the primary efficacy analysis will be used for these secondary efficacy analyses. Similar endpoints, where available, will be analyzed to compare OCA to historical controls as described below in Section 13.1.8.

Analyses of changes in liver biochemistry (GGT, ALT, AST, conjugated bilirubin, albumin, and INR) will be summarized and analyzed using the same methodology as specified in Section 13.1.4 for the key secondary analyses of change in ALP and total bilirubin.

Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as baseline TE, where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic (See Section 7.5.4). Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2).

Analyses of changes in MELD score, Child-Pugh score, MRS, IgM, CRP, TNF-α, FGF-19, CK-18, C4, and ELF score will be summarized and analyzed using the Wilcoxon Rank Sum Test to compare treatment groups. 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.

13.1.5.1. Association of Biochemistry with Clinical Outcomes and Clinical Benefit

The association between biochemistry including ALP and bilirubin with clinical outcomes will be assessed and the clinical benefit of OCA using biochemistry as a surrogate endpoint will be evaluated. Detailed analysis will be described in the SAP.

Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA using biochemistry as a surrogate endpoint for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.

13.1.6. Exploratory Efficacy Analyses

13.1.6.1. Responder Analyses

The percentage of subjects with a decrease in ALP of ≥15% and ≥40% from Baseline will be summarized by treatment group. In addition, the percentage of subjects with ALP ≤ULN will be summarized by treatment group.

The percentage of subjects that meet the criteria of a responder based on each of the definitions below will be summarized by treatment group. The response classification at baseline will also be included in the summary:

- ALP ≤3x ULN and AST ≤2x ULN and total bilirubin ≤ULN (Corpechot 2008)
- ALP ≤1.5x ULN and AST ≤1.5x ULN and total bilirubin ≤ULN (Corpechot 2011)
- ALP ≤1.67x ULN and total bilirubin ≤ULN (Momah 2012)
- Normal bilirubin (values ≤ULN) and normal albumin (values ≥lower limit of normal) (Kuiper 2009)
- ALP ≤1.76x ULN (Kumagi 2010)

Responder analyses will compare treatment groups using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor. Missing values will be considered as a non-responder.

13.1.7. Pharmacoeconomic and Health Outcomes Endpoints

Sufficient data will be collected on resource utilization and quality of life to undertake cost-effectiveness analyses that are relevant to the major countries taking part in this study. Resource utilization data on hospitalizations, healthcare provider visits, and medications will be combined with appropriate national unit costs to calculate a cost per patient per year in the study.

Quality of life data from patient-reported outcomes measures will be combined with survival data to calculate quality adjusted time in the study per patient. Cost-effectiveness analyses will report the incremental cost per major clinical outcome averted, liver-related death averted, life-year gained and quality-adjusted life year gained, including OCA as part of usual care versus usual care without OCA. Analyses will be conducted within the study and using a lifetime perspective. A separate economic analysis plan will be prepared and reported separately from this protocol.

13.1.8. Supportive Analysis

Per the International Conference on Harmonisation (ICH) E10 guidance, “where no obvious single optimal external control exists, it may be advisable to study multiple external controls”. In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, which serves as an external control for supportive analysis.

In an attempt to avoid the inherent biases with historical controls and to maintain the integrity of this comparison, one can invoke matching methods to optimize comparability and find a historical control that is “similar” to a participating subject. The historical database control should be as similar as possible to the study population and should have been exposed to a similar standard of care (see Section 5.5.2.3).

A propensity score can be used to reduce bias through matching, stratification, regression adjustment, or some combination. Propensity scores use information from a pool of patients who do not participate in the study (historical controls) to identify what would have happened to participating subjects in the absence of the treatment. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment between the treated subjects and the matched natural history subjects.

A full range of covariates across which the treatment and historical controls might differ will be considered to mitigate potential bias. Although the results of using matching controls are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained. Both UK-PBC Group and the Global PBC Study Group formally collect numerous covariates that could be used for propensity score estimation including standard of care, eg, UDCA.

Historical controls will be chosen based on the same inclusion/exclusion criteria where possible. Propensity scores will be estimated using the available covariates that predict receiving the treatment. Only covariates and not outcome variables will be included in the propensity score estimation, to avoid biased results that are in favor of one treatment.

The covariates and factors collected in the historical databases will be specified in the SAP.

Propensity scores will be estimated first through a logistic regression model with treatment group as the dependent variable and the above covariates/factors as independent variables. Then the stratum boundaries are determined based on the propensity score values for both groups (OCA population and control [historical and randomized placebo]) combined or in the OCA population or historical control group alone. Based on recommendations in the literature, quintiles of the estimated propensity score from the combined group will be used to determine the stratum boundary cut-offs for the different strata.

The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.

A third-party statistician(s) will perform the propensity score modeling and matching. This third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses. Outcome events collected in the historical database are: death (liver-related and all-cause), liver transplant, HCC, and other. Other is defined as cirrhosis or decompensation such as ascites, variceal bleed, and encephalopathy.

The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:

- Time to death (all-cause)
- Time to liver-related death
- Time to liver transplant
- Time to liver transplant or death (all-cause)
- Time to liver transplant or liver-related death

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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.

Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), using similar statistical methodology as specified above.

Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.

13.1.9. Handling of Dropouts or Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below. In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.

13.1.9.1. Time to Event Endpoints

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of investigational product dosing).

For analyses of the percentage of subjects with an event, subjects with no data after randomization will be considered to have an event.

All time to event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

13.1.9.2. Quantitative Endpoints

For efficacy endpoints that utilize an ANCOVA model, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward.

Sensitivity analyses of ANCOVA models will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

13.1.9.3. Responder Endpoints

In an efficacy analysis in which subjects are classified as either a responder or a non-responder (binary outcome) based on dichotomizing a continuous variable, any subject who does not provide an assessment at the specified timepoint for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator.

For sensitivity analyses using only "observed cases," subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

13.1.10. Multiple Comparisons/Multiplicity

The key secondary efficacy endpoints are as follows:

- Time to MELD score ≥15
- Time to first occurrence of liver transplant or death (all-cause)
- Change from Baseline in total bilirubin at end of study
- Change from Baseline in ALP at end of study

The hypothesis testing of key secondary analyses will compare placebo and OCA and will be conducted in a sequential closed testing gate-keeping procedure (in the order in which the key secondary endpoints are stated above), provided that the primary efficacy endpoint comparison is statistically significant in favor of OCA. If the primary comparison is not statistically significant then comparison of the secondary endpoints will be considered as descriptive and exploratory. This procedure controls the study-wise type I error.

- First (step 1) placebo and OCA will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to MELD score ≥15 will be compared between placebo and OCA (step 2). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- The time to liver transplant or death (all-cause) will be compared between placebo and OCA (step 3). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in total bilirubin will be compared between placebo and OCA (step 4). If the comparison achieves statistical significance at 2-sided 0.05 level in favor of OCA group, then
- Change from Baseline in ALP at the end of study will be compared between placebo and OCA (step 5).

If at any step defined above the comparison is not statistically significant at the 2-sided 0.05 level then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

Additional efficacy endpoints will be analyzed; however, hypothesis tests will be applied for descriptive and exploratory purposes only.

13.1.11. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. Subgroups will be assessed at Baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group).

Baseline subgroups of interest are as follows: age, age at PBC diagnosis, sex, race, body mass index, ALP level, bilirubin level, use of UDCA, years since diagnosis of PBC, and geographic region.

The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)

- Early (normal albumin and normal bilirubin)
- Moderate (abnormal albumin or abnormal bilirubin)
- Advanced (abnormal albumin and abnormal bilirubin)

The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.

- Monotherapy in patients who are intolerant or non-responsive to UDCA
- Elderly patients

Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.

Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.

13.1.12. Continuous Monitoring and Interim Analyses

Blinded safety reports including the accrual of events, drop outs, and/or loss of subjects to commercially available OCA will be reviewed by the DMC on a regular basis.

Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% (64 events) and 75% (96 events) of clinical outcome events, respectively.

The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy)

of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.

13.2. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population.

13.2.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities. Summary tables of treatment-emergent AEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group, and by severity and relationship to treatment. Tables of TEAEs leading to investigational product discontinuation and SAEs will be provided.

Adverse events of special interest as described in Section 12.1.1.4 will be summarized for each treatment group. In addition, each event is a component of the primary endpoint, and will be summarized as secondary endpoints as described in Section 13.1.4.

13.2.2. Clinical Laboratory Evaluations

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. Changes from pretreatment to each study visit will also be summarized by treatment group.

13.2.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Descriptive statistics of the vital sign and ECG parameters will be presented by treatment group and study visit, as well as the change from pretreatment at each visit.

13.2.4. Cardiovascular Adjudication Committee

In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).

13.3. 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 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 subjects. 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 subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate. Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects 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, Medical Dictionary for Regulatory Activities (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 subject safety, which alter the conduct of this study. The Investigators will inform the subjects of such actions and the protocol, patient information sheet (PIS), and consent will be revised, as appropriate.

13.4. Adjudication Committees

All suspected liver-related clinical outcomes, and MACE/Expanded MACE, 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 2 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

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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. 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 subject’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 CRF. The CRF 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 subject's medical records if these are deemed relevant to the performance, observations or conduct of this study.

14.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC 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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the CRF 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 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject 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 the Sponsor before he or she can enroll any subject 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 subjects to the ethics committee 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 subjects for the study. The protocol must be reapproved by the IRB or 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. 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, at a minimum annually, and after the study is complete.

16.2. 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.

16.3. Written Informed Consent

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

The subject's signed and dated ICF 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 subject.

16.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (eg, CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject'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 subject's names and identifying information (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet 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 subject number/randomization code/subject initials/site number, only.

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

The written ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IEC/IRB may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

17. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects 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 subjects, as applicable.

17.1. AE Reporting

The Investigator is responsible for recording AEs reported by the subject 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 Medical Monitor.

17.2. 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 subject's safety to be compromised if immediate action is not taken.

17.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/EC approvals (of protocol/amendments, subject questionnaires, etc)
- Form FDA 1572 or equivalent form for the Investigator's region
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

17.4. Ethics Review

Please see Section 16.1 for the Investigator's responsibilities regarding ethics review.

17.5. 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 subject medical files (retained per country specific regulations), completed study subject log and confidential subject 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 prior to 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.

18. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it sponsors consistent with the Declaration of Helsinki (Seoul Revision 2008, [http://www.wma.net/en/30publications/10policies/b3/index.html, accessed May 22, 2013]). 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 Study Registries (eg, 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 (when available) 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: The Sponsor, 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.

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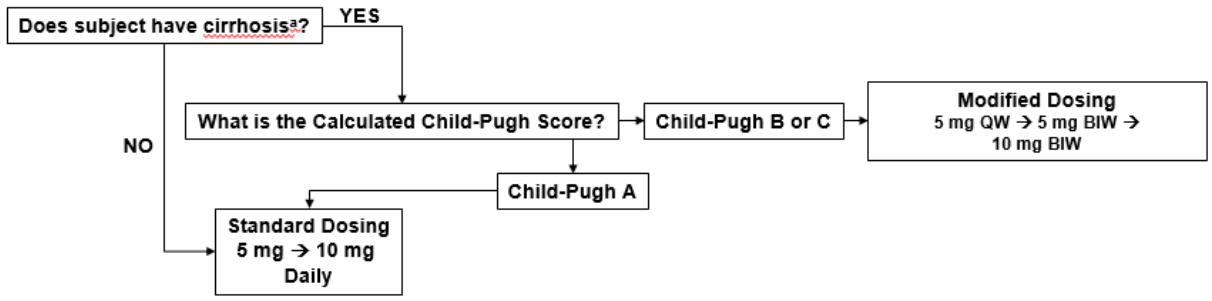
APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT

Subjects with cirrhosis and classified as Child-Pugh B or Child-Pugh C at Screening will follow a modified dosing schedule initiating 5 mg OCA or matching placebo once weekly as described in Figure 3. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly (Table 13).

Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).

Figure 3: Dosing by Cirrhosis Status and Child-Pugh Score



[a] Cirrhosis may be assessed by histology or non-histological methods as defined in Section 7.5.4.
BIW = twice weekly; QW = once weekly

Table 13: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score

	Modified Dosing Regimen for Child-Pugh B or Child-Pugh C
Starting Dose [a] (Day 0)	5 mg once weekly
Titration 1 [b] (≥Month 3)	5 mg twice weekly[c]
Titration 2 [b] (≥6 weeks after Titration 1)	10 mg twice weekly[c]

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

Dose Titration due to Change in Cirrhosis or Child-Pugh Score

When subjects demonstrate a change in cirrhosis status (as assessed per Section 7.5.4) or Child-Pugh Score (Section 7.5.5 dosing should be reassessed and the dosing regimen modified appropriately. Changes in Child-Pugh Score that result from a transient, explainable change in

laboratory parameters (eg, increase in INR due to vitamin K deficiency) should be documented appropriately and discussed with the Medical Monitor before any continuation or change to the dosing regimen.

Possible scenarios for dosing modifications include:

- Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C
- Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study

Subjects may titrate dose and dosing frequency up or down as appropriate, within the dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month and 2-Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.1 and Section 9.7.7).

Unscheduled Titration Visit, Optional Visit

An unscheduled up-titration visit may be scheduled for as early as 6 weeks after the initial titration visit (or subsequent titration visit) occurs for subjects who are following the modified dosing regimen. The visit procedures required for the unscheduled titration visit are outlined below. Subjects who up titrate at an unscheduled visit will continue to follow the regular visit schedule for all other study visits.

For subjects who up titrate at an unscheduled visit the following procedures will be performed:

- Assess and record AEs.
- Review and record concomitant medications.
- Perform the pre-Titration Tolerability Assessment as outlined in Section 7.4.1.
- Assess the subject's supply of investigational product to ensure an adequate amount. Access the IWRS and dispense investigational product if necessary.
- Provide the subject with a dosing diary to document his or her dosing.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - 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.

For subjects who up-titrate at an unscheduled visit: The ±1-week window related to the 2-month Post-Titration Visit can be modified to occur 2 weeks earlier or 2 weeks outside of the allowed visit window to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the 2-month Post-Titration Visit is performed during a regularly scheduled study visit, all scheduled procedures associated with that visit should be performed.

APPENDIX B. ETHICAL CONDUCT ACCORDING TO THE DECLARATION OF HELSINKI FOR COUNTRIES PARTICIPATING OUTSIDE THE US (DECLARATION OF HELSINKI, FORTELEZA, BRAZIL, 2013)

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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Online-Only Content: Audio podcast is available at www.jama.com.

APPENDIX C. REFERENCE LABORATORY VALUES FROM CENTRAL LABORATORIES

Covance Central Laboratories (Indianapolis, Indiana, US [for North America and Latin America regions]; Geneva, Switzerland [for Europe]; and Singapore [for Asia-Pacific region]) will serve as the central labs for analysis or specimen management for the analytes listed in the Table 12 of Protocol 747-302 Version 4. The following in text table provides the Covance Laboratory reference ranges for the pertinent liver biochemistries analyzed by Covance. These reference ranges are sex and/or age specific, and can change during the course of the clinical trial; therefore, investigative sites should always refer to the reference ranges available on the Covance issued laboratory reports.

		Covance Indianapolis		Covance Geneva and Covance Singapore	
Analyte	Sex	Age[a]	Reference Range	Age[a]	Reference Range
Albumin	Both	18Y – 69Y	SI Units: 33-49 g/L Conventional Units: 3.3-4.9 g/dL	18Y – 69Y	33-49 g/L
		69Y-80Y	SI Units: 33-46 g/L Conventional Units: 3.3-4.6 g/dL	69Y-80Y	33-46 g/L
		80Y-150Y	SI Units: 30-46 g/L Conventional Units: 3.0-4.6 g/dL	80Y-150Y	30-46 g/L
ALP	Female	18Y - 50Y	31-106 U/L	18Y - 50Y	31-106 U/L
		50Y - 60Y	35-123 U/L	50Y - 60Y	35-123 U/L
		60Y - 70Y	35-123 U/L	60Y - 70Y	35-123 U/L
		70Y - 80Y	35-123 U/L	70Y - 80Y	35-123 U/L
		80Y - 90Y	35–135 U/L	80Y - 90Y	35–135 U/L
		90Y – 150Y	35-140 U/L	90Y – 150Y	35-140 U/L
ALP	Male	18Y - 50Y	31-129 U/L	18Y - 50Y	31-129 U/L
		50Y - 60Y	35-131 U/L	50Y - 60Y	35-131 U/L
		60Y - 70Y	35-125 U/L	60Y - 70Y	35-125 U/L

		Covance Indianapolis		Covance Geneva and Covance Singapore	
Analyte	Sex	Age[a]	Reference Range	Age[a]	Reference Range
		70Y - 80Y	35-130 U/L	70Y - 80Y	35-130 U/L
		80Y - 90Y	35–125 U/L	80Y - 90Y	35–125 U/L
		90Y – 150Y	35-125 U/L	90Y – 150Y	35-125 U/L
ALT	Female	18Y – 69Y	6-34 U/L	18Y – 69Y	6-34 U/L
		69Y – 150Y	6-32 U/L	69Y – 150Y	6-32 U/L
ALT	Male	18Y – 69Y	6-43 U/L	18Y – 69Y	6-43 U/L
		69Y – 150Y	6-35 U/L	69Y – 150Y	6-35 U/L
AST	Female	18Y – 59Y	9-34 U/L	18Y – 59Y	9-34 U/L
		59Y – 150Y	9-34 U/L	59Y – 150Y	9-34 U/L
AST	Male	18Y – 59Y	11-36 U/L	18Y – 59Y	11-36 U/L
		59Y – 150Y	11-36 U/L	59Y – 150Y	11-36 U/L
Direct Bilirubin	Both	18Y – 150Y	SI Units: 2-7 umol/L Conventional Units: 0.1-0.4 mg/dL	18Y – 150Y	2-7 umol/L
Indirect Bilirubin	Both	0Y – 150Y	SI Units: 0-21 umol/L Conventional Units: 0.0-1.2 mg/dL	0Y – 150Y	0-21 umol/L
Total Bilirubin	Both	18Y – 150Y	SI Units: 3-21 umol/L Conventional Units: 0.2-1.2 mg/dL	18Y – 150Y	3-21 umol/L

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Y = years; SI=International System of Units

[a] The unstated word "to" is implied by the "dash" appearing in age specific reference ranges. A range such as "0-59 years" and "59-150 years" means: "0 up to but not including 59 years" and "59 up to but not including 150 years".

Source: Covance Laboratory Services Manual Version 5.0.0. Dates vary by region: 10 Nov 2016 (North America), 22 Nov 2016 (Europe and Singapore)

APPENDIX D. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1 (DATED 29 APR 2015)

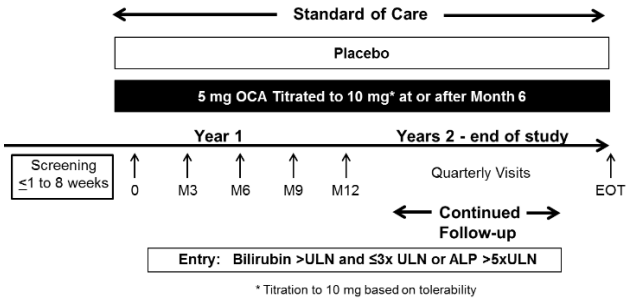
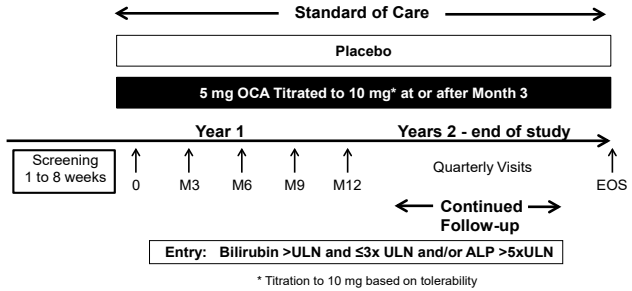
Rationale

The changes to the Original Version of the protocol, detailed below, modify the dose titration schedule based on observed efficacy and tolerability of OCA, address advice provided by regulatory agencies, and clarify questions raised by study site personnel currently using Original protocol version 1 dated 03 October 2014.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1. (Note: Differences are denoted in bold font; Minor formatting changes are not listed)

Section	Original Text	Revised Text
Title Page	Original: 03 October 2014	Original: 03 October 2014 **Amendment 1: 29 April 2015**
Procedures in Case of Emergency	**Procedures in Case of Emergency**	**Study Personnel Contact Information**
Or if Not Available	Contact**:** PPD **MD,** PPD **&** PPD **Development, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD	Contact**:** PPD **MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.** Telephone**:** PPD **(Pacific time zone)** Mobile**:** PPD Email**:** PPD
Synopsis	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **≤1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP)	Methodology This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC. Subjects will be screened during a **1** to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment alkaline phosphatase (ALP)

Section	Original Text	Revised Text
	and total bilirubin values (refer to Section 9.7.3). Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **6** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **6**-month visit or any subsequent study visit based on tolerability.  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	and total bilirubin values (refer to Section 9.7.3). **Mean values for ALP and total bilirubin will be calculated using all available screening values.** Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups. The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. Investigational product will be initiated at 5 mg OCA or matched placebo. After **3** months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the **3**-month visit or any subsequent study visit based on tolerability.  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

Section	Original Text	Revised Text
Synopsis	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5×ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved,** stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of contraception during the study and for 30 days after the end of treatment visit.	Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and/**or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects 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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
Synopsis	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12.	Exclusion Criteria **2.** History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>3. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

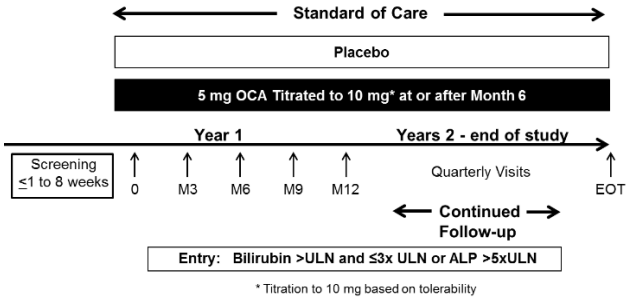
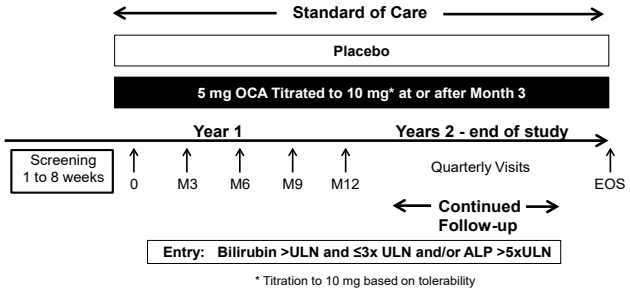
4. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of screening (pretreatment) QT</td><td>3. Mean total bilirubin >3× ULN

4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures

5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions such as chronic lymphatic leukemia)
5. Deleted text</td></tr>
<tr><td>Synopsis</td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life</td></tr></table></td><td>Criteria for Evaluation:<table><tr><td>Health outcomes and economics research</td><td>Including the following:
Cost-effectiveness and resource utilization
Quality of Life (Fatigue Impact Score and EQ-5D-5L)</td></tr></table></td></tr>
<tr><td>Synopsis</td><td>Statistical Methods: Other Efficacy Analyses
• Added text</td><td>Statistical Methods: Other Efficacy Analyses
• Development of varix/varices</td></tr>
<tr><td>4</td><td>List of Abbreviations
Added text</td><td>List of Abbreviations<table><tr><td>EOS</td><td>end of study</td></tr></table></td></tr>
<tr><td>5.4</td><td>As of 31 March 2014, OCA has been evaluated in the clinic in 18 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 March 2014, a total of 1023 subjects have received at least one dose of OCA and of these, 414 (40%) were subjects with PBC.</td><td>As of 31 January 2015, OCA has been evaluated in the clinic in 20 completed and ongoing studies, including subjects with other chronic liver diseases (eg, nonalcoholic steatohepatitis) and healthy subjects. As of 31 January 2015, approximately 1650 subjects have received at least 1 dose of OCA and of these, 432 were subjects with PBC with ≤5 years of OCA treatment.</td></tr>
</table>

Section	Original Text	Revised Text
	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 **up to 4 years.** The **LSTE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete	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**.** The **LTSE** phase of studies 747-201 and 747-301 are ongoing; the LTSE phase of Study 747-202 is complete
5.5.2.1	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated.	Rationale for OCA Doses … The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability **in the double-blind phase and after 3 months in the open-label phase)** and 10 mg; both treatment groups exhibited clinically meaningful improvements in liver biochemistry and were safe and generally well tolerated. **Based on these data, the intended commercial doses of OCA for the treatment of patients with PBC are 5 mg and 10 mg.** **The majority of efficacy results with OCA, in terms of change in alkaline phosphatase, was observed by 3 months and the time to treatment-emergent pruritus was typically 1 month or less in Study 747-301. As such, Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA if tolerated.**
5.5.2.2.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons.	Rationale for Control Groups; *Historical Control Group* Therefore, further evaluation of the effect of OCA will compare OCA treatment versus historical controls, and will be supportive to placebo comparisons **(ie, comparisons to historical and placebo controls will be evaluated separately)**.

Section	Original Text	Revised Text
5.6	**Additionally, consistent with nonclinical findings and the chemical characteristics of OCA (bile acid and detergent), an increase in liver function tests and hepatic AEs, including jaundice, were observed in subjects with liver disease at doses between 10 mg and 50 mg and in healthy volunteers who were treated at doses greater than 100 mg in Phase 1 multiple dose studies.** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). **The clinical significance of these lipid findings remains unclear and is being studied further.** Notably, **despite the observed decrease, HDL levels have generally remained within normal limits in subjects treated with OCA.**	• ***Deleted text*** **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 subjects with chronic liver disease such as PBC, hepatic findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed mainly at the highest dose of OCA (50mg daily).** Lipoprotein changes have also been observed with OCA dosing, including a decrease in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL). Notably**, in subjects 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 subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA-treated subjects with the exception of a modest transient and early rise after initiation of treatment.**
7.1	Overall Study Design …Subjects will be screened during a ≤1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3)….Following **6** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….	Overall Study Design …Subjects will be screened during a 1 to 8 week Screening period prior to entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) to confirm pretreatment ALP and total bilirubin values (refer to Section 9.7.3). ….Following **3** months of treatment with investigational product, subjects should be titrated in a blinded manner (ie, subjects randomized to OCA will increase their dose to 10 mg OCA) based on tolerability….

Section	Original Text	Revised Text
7.1.1	Study Design Diagram  **EOT = end of treatment**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal	Study Design Diagram  **EOS = end of study**; M = month; UDCA = ursodeoxycholic acid; ULN = upper limit of normal
7.1.2	Schedule of Trial Procedures Table 1: Schedule of Procedures ***1st column heading was "Screening Visit x2)*** ***Visit Window ≤1 to 8 wks …*** ***Visit window in 2nd column added new text*** ***Added text*** *Footnote a:* All subjects will have **two 2** bilirubin assessments at least 2 weeks apart including **those subjects who qualify based on ALP criteria. For subjects that do not qualify based on**	Schedule of Trial Procedures Table 1: Schedule of Procedures *Now 2 columns: 1st column now **"Screening Visit 1"*** *2nd column now **Screening Visit 2*** ***3** to 8 wks…* ***1 to 6 wks prior to Day 0*** ***Added Procedures:*** **Quality of Life Questionnaires (PBC-40, EQ-5D-5L, and FIS)** [g] (Day 0, Annually, EOT/EOS) **Endoscopy** [l] (Day 0, annually, per standard of care) **Hepatic Ultrasound** (Day 0, Annually, EOT/EOS) **Physical Exam and Assessments for Mayo Risk Score and Child-Pugh (**every 6 months**)** **Health Outcome Assessments** (All visits) ***Added Dose Titration at M3*** *Footnote a* All subjects will have **the chemistry panel retested to ensure subjects have 2 ALP and** bilirubin assessments at least 2 weeks apart **to calculate the mean result for both**

Section	Original Text	Revised Text
	ALP (ALP >5× ULN), the mean of the two **2** bilirubin assessments will be used to determine eligibility **(total bilirubin >ULN and ≤3× ULN).**	**analytes.** The mean of the **all screening ALP and** bilirubin assessments will be used to determine eligibility). **Samples for hematology and coagulation will not be collected at Screening visit 2**.
	Footnote b: The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2**,** and also 2 weeks post dose titration**,** to assess for AEs and concomitant medications and to verify that s/he is dosing as directed	*Footnote b:* The subject should be contacted by telephone on a monthly basis in between at-clinic study visits at Month 1 and Month 2 **(± 1 week),** and also 2 weeks post dose titration **(up or down)**, to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.
	Footnote e: Medical history at Screening will smoking and alcohol consumption history and current habits for both.	*Footnote e:* Medical history at Screening **and the yearly physical exam** will include **an assessment of** smoking and alcohol consumption history and current habits for both.
	Footnote g: **Subject Questionnaires include: Pruritus VAS, 5-D Pruritus Scale and Quality of Life questionnaires** (See Section 11.1.2.2 and Section 12.2.5.1)	*Footnote g:* **The EQ-5D-5L and FIS Quality of Life questionnaires are validated for use in multiple languages. If a validated translation is not available in the local language required for a specific study subject, the data from that questionnaire will not be collected.** (See Section 11.1.2.2 and Section 12.2.6)
	Footnote h: Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.	*Footnote h:* Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. **Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote i: ***Added text***	*Footnote i:* **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	Footnote j: ***Added text***	*Footnote j*: **Ultrasound will be conducted to enhanced HCC surveillance. If a lesion is found, a second confirmatory image (eg, MRI) should be obtained. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for these specific procedures.**
	*Footnote k***:** ***Added text***	*Footnote k:* **Child-Pugh Score will be calculated based on ascites assessment, hepatic encephalopathy grade, and central**

Section	Original Text	Revised Text
		laboratory evaluations per the Child-Pugh scoring system noted in the case report form. Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.
	Footnote l: ***Added text***	*Footnote l*: **Health Outcome Assessments: Data related to non-study related medical or surgical treatment procedures that the subject underwent and any medically relevant health care provider (HCP) or non-HCP related office visits that the subject attended should be collected throughout the study.**
	Footnote m: After **6** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.	*Footnote m:* After **3** months of treatment with investigational product, the dose should be increased (in a blinded manner) based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter. Titration above 10 mg OCA is not allowed.
	Footnote o: The subject should be instructed to fast overnight (at least 8 hours) prior to each visit**.** Fasting is required prior to all study visits, but water is permitted.	*Footnote o:* The subject should be instructed to fast overnight (at least 8 hours) prior to each visit **(except Screening visit 1).** Fasting is required prior to all study visits, but water is permitted.
	Footnote p: Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **site**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).	*Footnote p:* Urine β-hCG pregnancy tests must be performed in females of childbearing potential prior to entry. If positive, a confirmatory blood test must be performed at **the central laboratory**. If the blood test is also positive, the subject may not be enrolled in the study. (Additional testing may be conducted where required, regionally).
	Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change	***Other Footnotes may have changed symbols due to the additions above, but the content of the remaining footnotes did not change***
7.3	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **6** month study visit or at any study visit thereafter depending on tolerability.	Treatment Assignment Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the **3** month study visit or at any study visit thereafter depending on tolerability.
7.4	Dose Titration Criteria After **6** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched	Dose Titration Criteria After **3** months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA or matched

Section	Original Text	Revised Text
	placebo (in a blinded manner) at the **6**-month visit or any study visit following the **6**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.	placebo (in a blinded manner) at the **3**-month visit or any study visit following the **3**-month visit based on tolerability of investigational product. For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10-mg dose if tolerated.
7.4.1	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **her** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**. Early termination procedures should only be conducted if the subject withdraws consent.**	Safety Criteria for Adjustment or Stopping Doses If a subject reaches an event, **he** or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination**.**
7.5	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **subjects have completed the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the Study/Early Termination Visit.	Criteria for Study Termination As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the study before all **events have been accrued, and when subjects are still active on the study**. Investigators will be informed by the Sponsor as to when the final study visit is to be completed, and should then schedule all subjects for the **End of** Study Visit.
8.2	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN or an ALP >5× ULN 4. Either is not taking UDCA (**UDCA naïve or** no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a**n approved**, stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile), be prepared to use ≥1 effective **(≤1% failure rate)** method of	Subject Inclusion Criteria 2. A mean total bilirubin >ULN and ≤3× ULN **and**/or **a mean** ALP >5× ULN 4. Either is not taking UDCA (no UDCA dose in the past 3 months) or has been taking UDCA for at least 12 months with a stable dose for ≥3 months prior to Day 0 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or if premenopausal (and not surgically sterile),

Section	Original Text	Revised Text
	contraception during the study and for 30 days after the end of treatment visit.	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: • **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device (IUD); 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 subject)**
8.3	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. 3. **Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures** 4. Other medical conditions that may diminish life expectancy **to <2 years**, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia)	Subject Exclusion Criteria 2. History of liver transplant, current placement on a liver transplant list, or current MELD score >12. **Subjects who are placed on a transplant list despite a relatively early disease stage (for example, per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria** **3. Mean total bilirubin >3× ULN** **4. Subjects who have undergone gastric bypass procedures (gastric lap band is acceptable) or ileal resection or plan to undergo either of these procedures**

Section	Original Text	Revised Text
	5. **History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or prolongation of Screening (pretreatment) QT** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating	**5.** Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas *in situ* or other stable, relatively benign conditions such as chronic lymphatic leukemia) **5.** ***Deleted text*** 6. If female: plans to become pregnant, known pregnancy or a positive urine pregnancy test (confirmed by a positive serum pregnancy test **by the central laboratory**), or lactating
8.4.1	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test.	Reasons for Mandatory Discontinuation of Investigational Product … Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic **gonadotropin** (β-hCG) test **performed at the central laboratory.**
8.4.2	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent. The following events are considered **potential** appropriate reasons for a subject to discontinue investigational product;… • Withdrawal of Consent – ***Added text***	Other Reasons for Discontinuations of Investigational Product …Early termination procedures should only be conducted if the subject withdraws consent **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures)**. The following events are considered appropriate reasons for a subject to discontinue investigational product; … • Withdrawal of Consent – **Consent may be fully withdrawn** – **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 potential adjudicated hepatic and/or cardiovascular events**

Section	Original Text	Revised Text
	The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study.	The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study.
8.4.3	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the **end of treatment** (EOT) evaluations should be performed at the time of withdrawal, as appropriate.	Subject Discontinuation Notification The Investigator must notify the Sponsor study monitor by telephone **or email** as soon as possible if any subject prematurely withdraws from the study….This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the (EOT/**EOS**) evaluations should be performed at the time of withdrawal, as appropriate **(See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).**
9.1.1	Dose Adjustment Beginning at Month **6** After **6** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **6** visit, or at any study visit thereafter.	Dose Adjustment Beginning at Month **3** After **3** months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month **3** visit, or at any study visit thereafter.
9.2	Concomitant Medications Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Day 0**) and during the study must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the study.	Concomitant Medications 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 CRF, as well as any dose or dose regimen changes that occur during the study.
9.2.1	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing.	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 and encourage the discontinuation of open-label OCA therapy. However, if commercial OCA therapy remains, then investigational product should be discontinued to avoid potential double dosing. **Subjects that discontinue investigational product but continue commercial OCA therapy are expected to**

Section	Original Text	Revised Text
		continue through the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. Subjects will need to complete EOT procedures but continue with regularly scheduled visits until the study is terminated (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).
9.4	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.	Randomization and Blinding This study will be conducted in a double-blind, placebo-controlled manner. Allocation to 1 of 2 treatment groups (OCA or placebo) will occur on a 1:1 ratio across sites and will be stratified by UDCA treatment (yes/no) and **mean** baseline bilirubin categories (>ULN/≤ULN), as specified by the central laboratory.
9.4.1.	Unblinding Procedures – Emergency Unblinding Procedures • ***Added text - New section inserted.***	Unblinding Procedures – Emergency Unblinding Procedures **Treatment assignment for individual subjects will be made available to the Investigator for emergency use only 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 is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as unblinding which is necessary in order to treat an SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for**

Section	Original Text	Revised Text
		the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and the person or persons being informed about the unblinding. **The Data and Safety Monitoring Committee (DSMC) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.3 for further details regarding DSMC access to blinded and unblinded data. -The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS system to the appropriate named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.**
9.6	Restrictions **No additional restrictions.**	Restrictions **Participation in another investigation product, biologic, or medical device study within 30 days prior to Screening and during the course of the trial is prohibited.**

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>9.7.1</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Interval is ≤1 to 8 weeks prior to Day 0, allowing for 2 Screening 2 visits to repeat biochemistry tests, and ensuring ample time to receive lab results. The overall Screening interval is up to 56 days.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (7 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOT)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
</table>
EOT = end of treatment
</td><td>
<table>
<tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr>
<tr><td>Screening</td><td>Screening visit 1 interval is 3 to 8 weeks prior to Day 0 for screening visit 1. Screening visit 2 interval is 1 to 6 weeks prior to Day 0. The visit window for Screening 2 visits allows for the repeat biochemistry tests to be collected at least two weeks after the initial biochemistry sample was collected, and will ensure ample time to receive lab results. The overall Screening interval is up to 56 days, but screening procedures should not be performed during the last 7 days of the window.</td></tr>
<tr><td>Day 0</td><td>This is the day of randomization. On-treatment visit scheduling should be calculated from this point going forward. (The first dose of investigational product should be taken the next day, on Day 1.)</td></tr>
<tr><td>Months 3-12</td><td>±2 week (14 days)</td></tr>
<tr><td>Quarterly visits (Months 15 – EOS)</td><td>±2 weeks (14 days)</td></tr>
<tr><td>EOT
(When subject discontinues investigational product)</td><td>As soon as possible upon study discontinuation and as near as possible to the last dose taken</td></tr>
<tr><td>EOS
(When subject terminates the study)</td><td>The final study visit; EOS will occur concurrent with EOT if a subject discontinues investigative product at the time the subject’s</td></tr>
</table>
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Section	Original Text	Revised Text
		participation in the study ends (eg, withdrawal of consent or study termination by the Sponsor); EOS will occur after the EOT if the subject discontinues investigative product but continues in the study. EOT = end of treatment **EOS = end of study**
9.7.2	Informed Consent Procedures • ***Added text***	Informed Consent Procedures **Any change in a subject's consent status (eg, semi-annual telephone contact or medical record review) must be documented in a signed informed consent form or addendum. The subjects will be given a signed and dated copy of the consent document.**
9.7.3	Screening Procedures (≤1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed ≤1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months; however, all Screening procedures should be repeated and a new 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart **including those subjects who qualify based on ALP criteria**. • For subjects that do not qualify based on ALP alone (ALP >5×	Screening Procedures (1 to 8 Weeks prior to Day 0) Two Screening Visit assessments must be performed 1 to 8 weeks prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. **Screening Visit 1 will occur 3 to 8 weeks prior to Day 0; Screening Visit 2 will occur 1 to 6 weeks prior to Day 0, depending on the date that the first serum chemistry sample was collected.** Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects 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 3-digit Screening number assigned. • All subjects will have 2 bilirubin and ALP assessments at least 2 weeks apart • For subjects that do not qualify based on ALP alone (ALP >5× ULN), the mean of **all available (at least 2;**

Section	Original Text	Revised Text
	ULN), the mean of the 2 bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).	**including both scheduled and unscheduled)** bilirubin assessments will be used to determine eligibility (total bilirubin >ULN and ≤3× ULN).
	• Screening Visit procedures are as follows: • Record prior (if within 30 days of **Day 0**) and current concomitant medications • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual emission X ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**	• Screening Visit **1** procedures are as follows: • Record prior (if within 30 days of **Screening**) and current concomitant medications • ***Deleted text*** • ***Deleted text***
	• ***Added text***	**Screening Visit 2 procedures are as follows:** • **Verify inclusion and exclusion criteria for eligibility** • **Assess and record any pretreatment-emergent AEs** • **Record current concomitant medications** • **Verify that the subject has fasted for at least 8 hours**

Section	Original Text	Revised Text
		– **Record fasting status in the source and CRF** – **If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required prior to all study visits** • **Obtain blood samples for serum chemistry tests** • **The subject should be instructed to fast overnight (at least 8 hours) prior to next visit. Fasting is required prior to all study visits, but water is permitted.** • **In preparation for the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (selected study sites only), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.**
9.7.4	Day 0 Procedures (Randomization) • Subject questionnaires (see Section 12.2.5.1) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Day 0 Procedures (Randomization) • Subject **and Quality of Life** questionnaires (see Section **11.1.2.2** and Section **12.2.6**.) • Perform transient elastography (TE; at selected study sites, where available) using the Fibroscan® TE device**.** If TE has been done within **6** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. **If the TE cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**

Section	Original Text	Revised Text
	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.	• Conduct a DEXA bone density scan (at selected study sites, where available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. **If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If DEXA cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• *Added text*	• **Perform an esophagogastroduodenoscopy (endoscopy; at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices. If an endoscopy has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment endoscopy at Day 0 is not required. If the endoscopy cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.** – **Subsequent endoscopies should be performed annually or per standard of care and the Investigator's clinical judgment throughout the course of the study. Endoscopies should also be performed when platelet counts are <150 × 10^9 /L.**

Section	Original Text	Revised Text
	• ***Added text***	• **Perform an ultrasound (if equipment is unavailable, sites should make every attempt to use available community referral sites) for HCC surveillance. If an ultrasound has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment ultrasound at Day 0 is not required. If the ultrasound cannot be performed on Day 0 (e.g., device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, after subject eligibility has been confirmed.**
	• ***Added text***	• **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
	• ***Added text***	• **Review and** record prior concomitant medications
	• Record prior **(within 30 days of Day 0) and current** concomitant medications	• **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.**
9.7.6	Month 3 Procedures • ***Added text*** • ***Added text***	Month 3 Procedures • **Assess for dose titration, if eligible (refer to Section 7.4)** • **Obtain blood samples for:**

Section	Original Text	Revised Text
		– **OCA, C4, and FGF-19**
9.7.7	Month 6 Procedures • ***Added text***	Month 6 Procedures • **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** • **Mayo Clinic Score and Child-Pugh Assessment** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy**
9.7.8	Month 9 Procedures • ***Added text***	Month 9 Procedures • **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**
9.7.9	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.9), subjects who are participating in the PK assessment will each receive a single dose of investigational product **(10 mg OCA tablet)** with approximately 240 mL of water.	Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment Following collection of the Month 9 fasted samples (refer to Section 9.7.12), subjects who are participating in the PK assessment will each receive a single dose of investigational product (**blinded OCA or placebo tablet**) with approximately 240 mL of water.

Section	Original Text	Revised Text
	Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink.	Serial blood samples will be obtained for measurement of OCA and its conjugates prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. **Samples should be collected within a window of ±5 minutes of the scheduled sample time.** Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until the 4 hour sample is collected. Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink. **Samples will be stored for up to 5 years after the end of the study and will be destroyed after 5 years if not analyzed.**
9.7.10	Month 12 Procedures • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Procedures • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**

Section	Original Text	Revised Text
9.7.11	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) **Subjects should come to the study center for a quarterly study visit for a clinical laboratory evaluation to collect blood samples for calculation of MELD score. If the subject is not able to come to the study center for a visit, home visits may be arranged on a per subject basis**.	Month 3 and Month 9 Continued Follow-up Procedures ([±2 weeks]) • ***Deleted text*** • **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** • **Mayo Clinic Score and Child-Pugh Assessment**
9.7.12	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • ***Added text***	Month 6 Continue Follow-up Procedures (Semi-annually [±2 weeks]) • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**

Section	Original Text	Revised Text
9.7.13	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject questionnaires (see Section 12.2.5.1) • ***Added text***	Month 12 Continued Follow-up Procedures (Annually [±2 weeks]) • Subject **and Quality of Life** questionnaires (see **Section 11.1.2.2 and Section 12.2.6**) • **Perform an endoscopy (at selected study sites, where available) to assess the presence or absence of oesophageal varix/varices.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites)** • **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 physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** o **Presence/absence of peripheral edema** o **Presence (degree)/absence of ascites** o **Presence (degree)/absence of hepatic encephalopathy**
9.7.14	Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.	Early Discontinuation and/or Early Termination Procedures for Subjects that **Withdraw from Investigational Product or** Withdraw Consent Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will

Section	Original Text	Revised Text
		only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.
	Added text	**EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 7) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.**
	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination or discontinuation **(withdrawal of consent)**, an EOT visit must be performed as near as possible to her/his last dose of investigational product and the procedures, listed below, performed. … In these cases, the data will be recorded as EOT procedures in the CRF.	When a subject ends her/his participation in the study (eg, at a point between standard study visits) either due to early termination **(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. …. 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 **and EOS** procedures in the CRF.
	Added table	**Table 2: Early Discontinuation Scenarios**

Section	Original Text	Revised Text

	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 IP	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[b]	Telephone contact every 6 months (±2 weeks	Combined Visit, Completed as close as possible to last dose IP	

Section	Original Text	Revised Text
		[a] Refer to Section 7.1.2 Schedule of Study Procedures for all procedures and evaluations required at the End of Treatment and End of Study Visits. [b] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. No additional data (e.g. AE, concomitant medication, etc) data will be collected, except as indicated in Section 12.1.7**.**
	Some assessments noted below may be omitted if they have been completed within the **3** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.	Some assessments noted below may be omitted if they have been completed within the **6** months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing
	Prior to the EOT Visit:	Prior to the EOT/**EOS** Visit:
	During the EOT Visit: • Subject questionnaires (see Section 12.2.6) • Conduct a DEXA bone density scan (selected study sites); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable	During the EOT/**EOS** Visit • Subject **and Quality of Life** questionnaires **(see Section 11.1.2.2 and Section 12.2.6)** • Conduct a DEXA bone density scan (selected study sites**; not required at EOT/EOS if done within 6 months**); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable
	• ***Added text***	• Subject **and Quality of Life** questionnaires (see Section 11.1.2.2 and Section 12.2.6)
	• ***Added text***	• Perform TE (where available) using the Fibroscan® TE device (not required at EOT/**EOS** if done within 6 months)
	• ***Added text***	• Conduct a DEXA bone density scan (selected study sites; **not required at EOT/EOS if done within 6 months);** document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and

Section	Original Text	Revised Text
	• ***Added text***	medications for osteoporosis or osteopenia on the day of the scan, if applicable • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites); not required at EOT/EOS if done within 6 months** • **Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child-Pugh Assessments** – **Presence/absence of peripheral edema** – **Presence (degree)/absence of ascites** – **Presence (degree)/absence of hepatic encephalopathy** • **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**
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. ***[Added text]*** As appropriate, the Medical Monitor should be contacted.	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. **In the event of an inexplicable and acute (for example not explained by natural progression of the chronic disease) increase in alanine aminotransferase (ALT) to >3× baseline**

Section	Original Text	Revised Text
		(and >upper limit of normal [ULN]) or total bilirubin >2× baseline (and >ULN), the subject should be followed by repeat testing within 48 to 72 hours of the serum chemistry to confirm the abnormalities and to determine if they are increasing or decreasing. AE information should also be collected. If symptoms persist or repeat testing shows ALT >3× baseline (and >ULN) or total bilirubin >2× baseline (and >ULN), subjects should be followed until resolution of the abnormality and as clinically indicated depending on other laboratory and clinical signs and symptoms. As appropriate, the Medical Monitor should be contacted.
10.4	Investigational Product Preparation The investigational product will be provided in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects.	Investigational Product Preparation The investigational product will be provided **to the distribution center** in bulk bottles and therefore may be repackaged in unit dose form for administration to subjects **before shipping to the sites**.
11.1.2	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. Resource utilization information will be collected from CRFs such as number, type and duration of hospitalizations, number of outpatient physician visits (subject reported), and use of concomitant medications.	Secondary Assessments • Data will be collected to inform quality of life and cost-effectiveness analyses that are relevant to major health care systems around the world. **Quality of life will be assessed by questionnaires (PBC-40, EQ-5D-5L, and FIS) administered annually.** Resource utilization information will be collected **from the Medical and Surgical Treatment Procedures and Office Visit Log or other** CRFs such as number, type and duration of hospitalizations, number of

Section	Original Text	Revised Text
	• ***Added text***	outpatient physician visits (subject reported), and use of concomitant medications. • **Endoscopy will be conducted at selected study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline. Throughout the study, any endoscopy performed as part of the annual study assessments or standard of care will be collected in the case report form to assess for the development of varix/varices**
11.1.2.2	• Quality of Life questionnaires.	• Quality of Life questionnaires. **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:** **a. PBC-40: The PBC-40 (Jacoby 2005) 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.** **b. EQ-5D-5L: The Eq-5D-5L consists of 2 sections – the descriptive system and the visual analogue scales (VAS). 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 respondent's self-rate 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).**

Section	Original Text	Revised Text
		c. Fatigue Impact Score (FIS): The FIS is a validated 40-question questionnaire organized into 3 dimensions: cognitive, physical, and social. Each dimension has 5 levels: no problem, small problem, moderate problem, big problem, and extreme problem (Fisk 1994)
11.1.2.3	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.	• Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. **Subjects will be permitted to decline future analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation.** The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.
12.1.1.2	Serious Adverse Event • ***Added text***	Serious Adverse Event **Events <u>not</u> 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**

Section	Original Text	Revised Text
12.1.4.2	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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 investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports received from the Sponsor to her/his local IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).	Reporting of Serious Adverse Events PPD **MD** **Tel:** PPD **(Pacific time zone)** **Mobile:** PPD **Email:** PPD All SAEs **occurring while subjects are receiving investigational product or are on an investigational product holiday** (including Potential Clinical Outcome Events that qualify as serious) must be reported to the medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE…. 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. **A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).** The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) safety reports (SUSARs) that occur during the study within the time frames required by each regulatory agency. The Investigator is responsible for submitting information on IND safety reports/**SUSARs** received from the Sponsor **or Sponsor designee** to her/his local **EC**/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).

Section	Original Text	Revised Text
12.1.6	Notification of Post-Study SAEs • ***Added text***	Notification of Post-Study SAEs **SAEs that occur more than 30 days after a subject has discontinued investigative product, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with investigative product, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.**
12.1.8	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments.	Pregnancy and Follow up Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. **The Sponsor may also follow the health of an infant born subsequent to use of investigational product.**
12.2.2	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page ….	Physical Examination … Any clinically significant abnormality should be reported on the AE CRF page **for findings that appear after consent, and on the medical history CRF for any finding present prior to consent**….
12.2.5.1	**12.2.5.1** Subject Questionnaires	**12.2.6** Subject Questionnaires
12.2.6/**12.2.7**	**12.2.6** Laboratory Assessments **Subjects testing positive for urine drug screen will be excluded from the study.**	**12.2.7** Laboratory Assessments ***Deleted text***

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>Table 4 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, thyroid hormones (T3, T4, TSH)</td></tr>
</table></td><td>Table 5 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 (BUN), 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 very low density lipoprotein [VLDL] fractions and triglycerides[TG]), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids</td></tr>
</table></td></tr>
<tr><td>12.2.6</td><td>Laboratory Assessments
• Added text

MELD scores, Child-Pugh score and MRS will be calculated at quarterly visits based on serum chemistry and coagulation.</td><td>12.2.7 Laboratory Assessments
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.

MELD scores, Child-Pugh score and MRS will be calculated at quarterly (MELD scores only) and semi-annual visits based on serum chemistry and coagulation.</td></tr>
<tr><td>13.1.5</td><td>Additional Secondary Efficacy Analyses
• Added text</td><td>Additional Secondary Efficacy Analyses
• Time to development of varix/varices</td></tr>
</table>

Section	Original Text	Revised Text
13.1.8	Supportive Analysis Although the results of using matching are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.	Supportive Analysis Although the results of using matching **controls** are conditional only on the observed covariates, if one has the ability to measure many of the covariates that are believed to be related to the treatment assignment, then one can be fairly confident that approximately unbiased estimates for the treatment effect can be obtained.
13.3	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. **In addition, the DSMC statistician will evaluate the sample size as described in Section 13.1.2.1**. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study.	Data and Safety Monitoring Committee The DSMC will review data on a periodic basis to ensure the safe and proper treatment of subjects. Based on review of these data, the DSMC will advise the Sponsor on the validity and scientific merit of continuing the study. The DSMC operates under an appropriate charter (in compliance with relevant regulatory guidance) that defines its organization and operation and includes specific procedures for each study. The DSMC will prepare written minutes of both its open and closed sessions for each study. **The DSMC will document details about any unblinded subject data reviews in the closed session DSMC minutes, which will be made available to the Sponsor only after the database is locked and the trial is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DSMC.**

Section	Original Text	Revised Text
16.2, Ethical Conduct of the Study	Ethical Conduct of the Study The study will be performed in accordance with ethical principles **that have their origin in the Declaration of Helsinki (Seoul Revision, 2008**) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.	Ethical Conduct of the Study The study will be performed in accordance with ethical principles and are consistent with ICH/GCP, **local** applicable regulatory requirements **(in addition to Appendix C)** and the Sponsor's policies.
19	List of References • Added text	List of References Fisk JD, Ritvo PG, Ross L, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994 Jan;18 Suppl 1:S79-83. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36. Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut. 2005;54(11), 1622-1629. Oemar M, Janssen B. EQ-5D-5L User Guide: Basic Information on how to use the EQ-5D-5L instrument. 2013 October;Version 2.0:1-28.
Appendix C	• **Added document**	Ethical Conduct according to the Declaration of Helsinki for Countries Participating Outside the US

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 (DATED 12 NOV 2015)

Rationale

The changes to Amendment 1 of the protocol, detailed below, generated specifically for regulatory authority requests, include an additional exclusion criteria and changes to text precluding UDCA naïve subjects from entering the study and clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, thus answering questions raised by regulatory authorities.

Summary of Changes

The following revisions were made to protocol 747-302 under Amendment 1.1. (Note: Revised text in Amendment 1.1 is indicated in bold font, and the text deleted from Protocol Amendment 1 is crossed out in the table below. Minor formatting changes are not listed.)

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
Title Page	Original: 03 October 2014 Amendment 1: 29 APRIL 2015	Original: 03 October 2014 Amendment 1: 29 **April** 2015 **Amendment 1.1: 12 November 2015**
Study Personnel Contact Information	~~Mobile: PPD (Pacific time zone)~~ Telephone: PPD ~~Telephone~~ PPD	(deleted) Telephone: PPD (deleted)
Synopsis, Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
Synopsis, Statistical Methods: Sample Size Justification	• ~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)
8.3 Subject Exclusion Criteria	(insertion)	**14. UDCA naïve (unless contraindicated)**
9.2 Concomitant Medications	(insertion)	**The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile**

Section	Original Text (Amendment 1, 29 April 2015)	Revised Text (Amendment 1.1, 12 November 2015)
		of caffeine, a sensitive CYP1A2 substrate, 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.
12.1.4.2 Reporting of Serious Adverse Event	~~Mobile: PPD (Pacific time zone)~~ Telephone: +1 ~~858 964 1571~~	(deleted) Telephone: PPD
13.1.2 Determination of Sample Size	~~5% of the subjects will have never been treated with UDCA; 95% of the subjects will have been on UDCA for at least 1 year~~	(deleted)

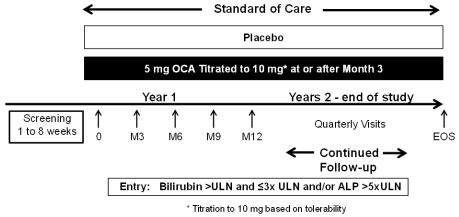
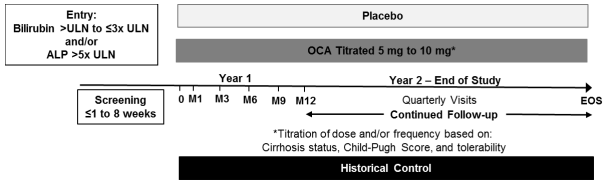
APPENDIX F. SUMMARY OF CHANGES: PROTOCOL AMENDMENT 1.1 TO VERSION 3 (DATED 07 SEP 2016)

Rationale

The changes to Version 3 of the protocol, include dosing adjustments based on Child-Pugh scoring, additional exclusion criteria, changes to text precluding UDCA-naïve subjects from entering the study.

Please note that the Sponsor has renamed protocol "amendments" to "versions", therefore all future revisions that require a revised protocol will have an associated "version" number. The table below includes substantial revisions made to Protocol 747-302 under Version 3, which encompass the revisions captured in Protocol Amendment 1.1. Revised text in Version 3 is indicated in bold font, and the text deleted from Protocol Amendment 1.1 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 (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	... ~~Mean values for ALP and total bilirubin will be calculated using all available screening values. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized (1:1) to OCA or placebo treatment groups.~~ The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ULN). Investigational product (OCA or matched placebo) will be taken orally, once daily. ~~Investigational product will be initiated at 5 mg OCA or matched placebo. After 3 months of treatment with investigational product, the dose may be increased (to the maximum dose of 10 mg OCA or matched placebo, in a blinded manner) at the 3-month visit or any subsequent study visit based on tolerability. Subjects will be seen at quarterly visits for the duration of the study.~~	... Investigational product will be taken orally, once daily **for the majority of subjects; dose and frequency will be modified for subjects with cirrhosis (including subjects progressing to cirrhosis during the study) and classified as Child-Pugh B or C.** The randomization will be stratified by ursodeoxycholic acid (UDCA) treatment (yes/no) and baseline bilirubin categories (>upper limit of normal [ULN]/ ≤ ULN).	To incorporate a dosing and titration regimen based on subject's Child-Pugh Scores, to align with the recommended dosing regimen found in the Ocaliva US Package Insert for patients with hepatic impairment.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology. 7.1.1, Study Design Diagram, Figure 1	Schematic diagram 	Updated schematic diagram  **Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for subjects classified as Child Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration**	Incorporate updated dosing scheme to reflect addition of Child-Pugh scoring.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Synopsis, Methodology	(insertion)	**Dosing frequency will be determined by the presence or absence of cirrhosis and, if cirrhosis is present, by Child-Pugh Score as described below:** **• Non-cirrhotic subjects or subjects classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.** **• For those subjects that up-titrate to 10 mg, dosing may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, based on tolerability). Subjects may be titrated back to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator.** **• Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5-mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability.** **Includes New Table: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Revised methodology to incorporate the changes in dosing for subjects based on the Child-Pugh Scores.
5.1, Overview	(insertion)	**The United States Food and Drug Administration (FDA) has granted accelerated approval for Ocaliva for the treatment of PBC. Ocaliva is not yet approved outside the United States for use in any indication**.	Language updated as OCA is approved in the US with the trade name Ocaliva.

5.5.2.2, Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment	(Insertion)	**New section: Rationale for Modified OCA Doses in Patients Classified with Child-Pugh B or Child-Pugh C Hepatic Impairment** **Simulations using a physiologic PK model predicted changes in systemic and liver OCA concentrations associated with changes in the severity of hepatic impairment (Child-Pugh score). Model simulations predicted that for mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, total OCA plasma concentrations increase 1.4-, 8.0-, and 13-fold relative to subjects 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 (Child-Pugh B and C) subjects treated with OCA in phase 1 and 2 studies experienced plasma OCA exposures >10-fold higher than those in healthy subjects, 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. Collectively, the results from these analyses and those from bile acids in the literature suggest that the doses of OCA administered to hepatically-impaired patients should be modestly lower than those for patients with normal hepatic function to achieve similar hepatic exposure.** **Per the approved FDA prescribing label, the recommended dosing regimen for OCA in subjects with moderate and severe hepatic impairment is a starting dose of 5-mg OCA once weekly. Dosage adjustments in subjects with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment may be made after establishing tolerability at the lower dose**	Provide the rationale to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores into the protocol.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		(full modified dosing regimen is described in Appendix A).	
5.6, Summary of Known Potential Risks with OCA	(Insertion)	**…These findings were seen more frequently with doses above 10 mg OCA. In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.**	Added two AE terms reported in the updated Investigator's Brochure.
7.1, Overall Study Design	…~~Investigational product will be initiated at 5 mg OCA or matched placebo.~~ Following 3 months of treatment with investigational product, ~~subjects~~ should be titrated ~~in a blinded manner (ie, subjects randomized~~ to ~~OCA will increase their dose to~~ 10 mg OCA) based on tolerability	Investigational product will be taken orally, once daily**. Subjects who are non-cirrhotic or classified as Child-Pugh A at Screening will initiate investigational product once daily with 5-mg OCA or matching placebo.** Following 3 months of **once daily** treatment with investigational product, **the dose** should be titrated **to a maximum** 10 mg OCA **or matching placebo once daily**, based on tolerability (see Section 7.3). **Subjects with cirrhosis and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, and will initiate investigational product once weekly with the 5-mg OCA or matching placebo dose. In addition, these subjects will follow a modified titration plan, which is outlined in Appendix A.**	Amend the protocol to incorporate a dosing and titration regimen based on subject's Child-Pugh Scores.
7.1.2, Table 1, Schedule of Study Procedures – Screening to Month 12 (Table 1 of 2), 9.3, Treatment compliance	~~Safety Contact~~	This visit has been deleted.	Replaced with the 1 Month Post-Titration Visit.
	(Insertion)	Added the following visits: • Month 1 • 1 Month Post-Titration Visit	Visits were added to accommodate the updated dosing and titration regimen based on subject's Child-Pugh Scores.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	[b]~~The subject should be contacted by telephone on a monthly basis in between at clinic study visits at Month 1 and Month 2 (± 1 week), and also 2 weeks post dose titration (up or down), to assess for AEs and concomitant medications and to verify that s/he is dosing as directed.~~ [e]~~As soon as possible upon study discontinuation and as near as possible to last dose taken.~~ [n]~~Subject to begin dosing on Day 1~~	Deleted.	Result of table being updated for the dosing and titration regimen based on subject's Child-Pugh Scores.
	(Insertion)	Added the following study procedures: • Cirrhosis Status Assessment[e] • Assessments for Child-Pugh Scores[g] • Dose Titration: Standard Dosing[n,o] • Dose Titration: Modified Dosing [n,o] • Dosing Diary	Study procedures were added to accommodate the updated dosing/titration regimen. Dosing diary was added to improve compliance.

	(Insertion)	Added the following footnotes: • **[b]Safety Post-Titration visits must be performed 1 month + 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.** • **[e]Presence or absence of cirrhosis should be assessed per Section 9.7.3. Cirrhosis status should be repeated as clinically indicated.** • **[f]Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF.** • **[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.** • **[n]Pre-titration tolerability assessment, which include a review of AEs and a review of safety laboratory results (eg, chemistry, hematology, and coagulation), must be completed by the Investigator before any up-titration can occur as defined in Section 7.4.1. Lab results obtained within 2 months prior to any up-titration may be used for assessment.** • **[o]Dose Titration is based on cirrhosis status (Section 9.7.3) and Child-Pugh score (Section 7.3). The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. Subsequent dose titration(s) for**	Added footnotes provide clarity regarding assessments and visits based on the evaluation of Child-Pugh scores.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		subjects who are classified as Child-Pugh B or Child-Pugh C and following a modified dosing schedule may occur no earlier than 6 weeks after the previous dose titration. For complete modified dose titration criteria, refer to Appendix A. • **[p]Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1) and to take investigational product at approximately the same time of day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet**.	
7.1.2, Table 2, Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)		**New table- Schedule of Study Procedures – Year 2 Through End of Study (Table 2 of 2)**	Divided Schedule of Study Procedures into 2 tables, updated to include visits added per updated dosing/titration information.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.3, Planned Dosing Regimen	7.3 ~~Treatment Assignment~~ ~~Subjects will receive either placebo or 5 mg OCA and should titrate to 10 mg OCA (in a blinded manner) at the 3-month study visit or at any study visit thereafter depending on tolerability.~~	**7.3 Planned Dosing Regimen** Subjects will **be randomized to treatment with** either **OCA or matching placebo in a 1:1 ratio. Subjects will be dosed according to their cirrhosis status (as defined in Section 9.7.3) and applicable Child-Pugh Score (see Section 9.7.4) as outlined in Table 3.** **Subjects who are non-cirrhotic or classified as Child-Pugh A at screening will receive 5-mg OCA or matching placebo once daily for 3 months. Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. A review of safety laboratory results (eg, chemistry, hematology, and coagulation) obtained no more than 2 months prior to the planned up-titration visit must be completed as part of the product tolerability assessment before up-titration can occur (see Section 7.4.1).** **For those subjects that up-titrate to 10 mg, dose may be decreased to 5 mg at any time during the study as considered clinically appropriate (eg, tolerability). Subjects may be titrated back up to a maximum dose of 10 mg once daily based on tolerability and clinical judgment of the Investigator. A review of safety laboratory results obtained within 2 months of the planned up-titration visit date is not required prior to re-challenging a subject up to 10 mg once daily dosing, as long as the decrease in dose/dosing frequency was less than 3 months in duration.**	Section renamed to reflect changes in titration and dosing for subjects with hepatic impairment.
	(Insertion)	**New: Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score**	Tables added to clarify changes in titration and dosing.
		New: Table 4: Determination of Dosing Regimen	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.4 Dose Titration Criteria	~~After 3 months of treatment at the 5 mg dose, the dose of OCA will be increased to the maximum dose of 10 mg OCA~~ or ~~matched placebo (in a blinded manner) at the 3 month visit or any study visit following the 3 month visit based on~~ tolerability ~~of investigational product~~. ~~For those subjects that increased their dose to 10 mg, they may decrease his or her dose to 5 mg at any time during the study as considered appropriate (eg, tolerability), but should be titrated back to 10 mg based on tolerability and clinical judgment by the Investigator as soon as possible with the goal that all subjects remain on the 10 mg dose if tolerated~~	**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 subject's cirrhosis status (using histology or non-histological methods as defined in Section 9.7.3 and Section 9.7.4) or Child-Pugh Score.** **Scheduled Dose Titration - The first dose titration for any subject may occur no earlier than 3 months following initiation of OCA or matching placebo. Subsequent titrations in dose or dosing frequency for subjects following the Modified Dosing Regimens may occur no earlier than 6 weeks (via an unscheduled visit or regular visit- see Appendix A) following an up-titration.** **Tolerability Dose Titration - Investigators** may decrease **the dosing frequency** or dose **for any subject** at any time during the study, as considered **clinically** appropriate (eg, tolerability; **see Section 7.4.2).** **Dose Titration due to Change in Cirrhosis or Child-Pugh Score - When subjects demonstrate a change in cirrhosis status (as assessed per Section 9.7.3) or Child-Pugh Score (Section 9.7.4), dosing should be reassessed and the dosing regimen modified appropriately. Changes to the dosing regimen are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. Table 5 provides an overview of the possible changes in dosing regimen due** to **changes in cirrhosis or Child-Pugh 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.**	Entire section revised to reflect changes in titration and dosing.
7.4 Dose Titration Criteria	(Insertion)	**New: Table 5: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score**	

7.4 Dose Titration Criteria	(Insertion)	**Subjects who exhibit development of cirrhosis at any point in the study should be assessed per Section 9.7.3. If the presence of cirrhosis is confirmed and the subject's Child-Pugh score is either B or C, the appropriate modified dosing regimen should be followed. The dose or frequency of investigational product should be down-titrated to the next lowest dosing frequency in the appropriate modified dosing regimen unless the subject is currently taking a dose and frequency also specified in the modified dosing regimen and the investigator determines that it is clinically appropriate for the subject to continue at that dose (Appendix A).** **Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study should also have their dosing modified per the appropriate dosing regimen (Appendix A).** **Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section 7.4.1.** **Child-Pugh Scores will be calculated at all quarterly study visits. All associated visit data (including central laboratory results) should be entered into the eCRF in a timely fashion to confirm that the subject's Child Pugh Score has not changed. If a change in cirrhosis status (as defined in Section 9.7.3) and/or Child-Pugh Score is observed independent of a study visit, the subject 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 and table added to provide dosing guidelines to investigators.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		Subjects' dose and dosing frequency may be titrated up or down within the appropriate dosing regimen based on the calculated Child-Pugh Scores. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments.	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
7.4.1, Pre-Titration Tolerability Assessment Requirements	(Insertion)	**7.4.1 Pre-Titration Assessment Requirements** **Tolerability of investigational product must be assessed prior to titrating a subject to a higher dose. A review of adverse events and safety laboratory results (eg, chemistry, hematology, and coagulation) obtained within 2 months of the up-titration visit must be performed as part of the investigational product tolerability assessment, prior to any planned up-titration in investigative product (eg, Month 3, Month 6). Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the 1 Month Post-Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are acceptable for review purposes; however, 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 subject to a higher dose.** **To be eligible for a dose up-titration:** **• Subjects 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.** **• There must be no clinically significant increase (as determined by the investigator) in the subject's liver function tests. Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19, should be implemented, as required**	Section added to provide guidance for assessing subject tolerability prior to titration.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
8.4.2, Other Reasons for Discontinuation of Study or Investigational Product	(Insertion)	• **Subject begins treatment with commercially available OCA** **… safety concerns and related to study drug** • Consent may be fully withdrawn **(in which case the subject discontinues both investigational product and study visits and procedures)** **…Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.**	Added text as Ocaliva is commercially available in the US and therefore subjects may be discontinued if they began off-study treatment with Ocaliva.
8.4.2.1, Elevated Liver Enzymes	(Insertion)	**New Section: 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.**	Section added to incorporate monitoring of liver test results during the study.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.1, Investigational Product Treatment Regimen	~~**9.1.1 Dose Adjustment Beginning at Month 3**~~ ~~After 3 months of treatment with investigational product, the dose of investigational product should be increased in a blinded manner and based on tolerability; this may occur at the Month 3 visit, or at any study visit thereafter. Titration above 10 mg OCA is not permitted~~.	**At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the Month 9 PK assessment, must be completed before administration of investigational product.**	Section revised to reflect changes in titration and dosing.
9.2, Concomitant Medications	Subjects taking bile acid sequestrants (BAS) 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).	New sub-heading**:** ***Drug Interactions*** Subjects 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 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.** (…) **Information related to additional drug-drug interaction (DDI) studies is available in the current version of the Investigator's Brochure (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 with OCA that may be observed in study subjects.**	Section revised to provide additional information on drug-drug interactions with OCA.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.2.1, Prohibited Medications	… the Investigator should be cognizant of the possibility of double dosing ~~and encourage the discontinuation of open-label OCA therapy. However, if~~ commercial OCA therapy ~~remains, then investigational product should be discontinued to avoid potential double dosing~~. ~~Subjects that discontinue investigational product but continue commercial OCA therapy~~ are expected to continue through the end of the study, ~~and~~ the …	… the Investigator should be cognizant of the possibility of double dosing. **Subjects who continue with** commercial OCA therapy **must** discontinue **investigative product and** are expected to continue through the end of the study. …	Ocaliva is commercially available in the US and, therefore, subjects wishing to take commercially available drug are not discouraged, but they must discontinue investigative product.
9.7.1, Visit Windows	(insertion)	**Added the following visit windows:** • **Month 1 (+1 week [7 days])** • **Titration Visit – Standard Dosing Regimen (≥Month 3)** • **Titration Visit 1 – Modified Dosing Regimen (≥Month 3)** • **Titration Visit 2 – Modified Dosing Regimen (≥6 weeks after Titration Visit 1)** • **Titration Visit 3 – Modified Dosing Regimen (Child-Pugh B ONLY) (≥6 weeks after Titration Visit 2)** • **Post-Titration Visit, (+1week [7 days]) from date of titration or after ≥3 months at a decreased dose or frequency)**	Added visits to accommodate the updated dosing/titration scheme.

9.7.3, Assessing Cirrhosis	(Insertion)	**New: 9.7.3. Assessing Cirrhosis** **To determine which dosing regimen subjects should follow, the presence or absence of 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 is defined as a subject 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/mm3) with:** **– persistent decrease in serum albumin, or** **– elevation in prothrombin time /INR (not due to antithrombotic agent use), or** **– elevated bilirubin (2× ULN)** **Subjects who exhibit no evidence of cirrhosis by the above methods of assessment will be dosed using the Standard Dosing Regimen, while those who do exhibit evidence of cirrhosis by one or more of the above methods will be dosed using the Modified Dosing Regimen according to their Child-Pugh Score calculated in the electronic case report form (eCRF) (see Appendix A).** **Cirrhosis status should be reassessed as clinically indicated throughout the study. Any change in**	Added section to assess cirrhosis as this assessment will determine the acceptable dosing regimen based on a subject's Child-Pugh score.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		cirrhosis status will necessitate re-evaluation of the dosing regimen.	
9.7.4, Child-Pugh Score	(Insertion)	**9.7.4. Child-Pugh Score** **Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF adding the scores from the 5 factors outlined in Table 6 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 Child-Pugh 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.** **It is important to note that subjects must have confirmed cirrhosis as assessed by one or more of the above criteria (Section 9.7.3) prior to applying the calculated Child-Pugh score for dosing. Investigators will be responsible for determining the appropriate dosing regimen based on both the cirrhosis status and the Child-Pugh score (Table 6). Any change in cirrhosis status or Child-Pugh Score will necessitate re-evaluation of the dosing regimen**	Section added to provide Investigators with information on the Child-Pugh scoring system.
9.7.4, Child-Pugh Score	(Insertion)	**Table 6 (New) Child-Pugh Scoring System**	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.6, Screening Procedures (1 to 8 Weeks prior to Day 0)	(Insertion)	The following procedures were added: Screening Visit 1 procedures are as follows: • **Provide the subject with a dosing diary to document his or her dosing** • **Assess for the presence/absence of cirrhosis** • **Perform status assessment for calculation of Mayo Risk Score** Screening Visit 2 procedures are as follows: • **Perform an ultrasound for hepatocellular carcinoma (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 Visit 2, and a report/adequate data are available, a pretreatment ultrasound at Screening Visit 2 is not required. If the ultrasound cannot be performed at Screening Visit 2 (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.**	Procedures added to assess cirrhosis.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.7, Day 0 Procedures (Randomization)	9.7.4. ~~Day 0 Procedures~~ ~~• Perform an ultrasound for hepatocellular carcinoma (HCC) surveillance (if equipment is unavailable, …~~ ~~• Perform physical examination and overall status assessment for calculation of Mayo Risk Score and Child Pugh Assessments.~~ ~~□ Presence/absence of peripheral edema~~ ~~□ Presence (degree)/absence of ascites~~ ~~□ Presence (degree)/absence of hepatic encephalopathy~~	9.7.**7**: Day 0 Procedures (Randomization) • **Provide the subject with a dosing diary to document his or her dosing.**	Updated visit to accommodate the updated dosing/titration scheme.
9.7.8, Month 1 Procedures	9.7.5 Safety Contact (Month 1, Month 2, and 2 Weeks Post-Titration [by telephone])	9.7.**8** Month 1 Procedures • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:** - **At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, …** - **If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. …**	Revised section to include the new Month 1 visit procedures.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
9.7.9, Month 3 procedures, 9.7.11, Month 6 Procedures, 9.7.12, Month 9, 9.7.14, Month 12 Procedures	(Insertion)	• **Perform assessments for calculation of Child-Pugh Score**	Added procedure to accommodate the updated dosing/titration scheme.
9.7.9 thru 9.7.17	(Insertion)	**If up-titration will occur at this visit, complete the pre-titration visit and visit related assessments as outlined to ensure all procedures required for dose titration eligibility have been met, including the required review of the dose titration laboratory parameters.** • **Provide the subject with a dosing diary to document his or her dosing** • **… review dosing diary with the subject**	Text added to clarify procedures required before up-titration.

9.7.10, Post Titration Visit Procedures	(Insertion)	New**: 9.7.10. Post Titration Visit Procedures** • **Assess and record AEs.** • **Review and record concomitant medications.** • **Assess investigational product compliance, perform investigational product accountability, and review dosing diary with the subject.** • **Obtain blood samples for serum chemistry, hematology, and coagulation tests.** • **Provide the subject with a dosing diary to document his or her dosing.** • **In the event it is not feasible for the subject to return the site for the above referenced procedures, the following alternative visit procedures are available, to help ensure compliance with the Post-Titration visit requirements:** **- At the Up-titration Visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Post-Titration visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance.** **- If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review**	Added visit to accommodate the updated dosing/titration scheme.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		concomitant medications, and assess investigational product compliance. • **Schedule the next visit, reiterate dosing instructions, and advise the subject:** **- 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…**	
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	(Insertion)	**…Subjects who are following the Child-Pugh B and Child-Pugh C modified dosing regimen may participate in the PK assessment and will dose in the clinic at this visit even if the previous dose was taken less than 3 days prior; however, every attempt should be made to schedule the Month 9 PK visit according to the subject's established dosing schedule**.	Clarify that subjects with hepatic impairment may continue to participate in the PK assessment.
9.7.13, Month 9 Procedures for Subjects Participating in Pharmacokinetic Assessment	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink…	…Lunch will be provided following collection of the 4 hour PK sample; the lunch will be a meal replacement drink **with no other food allowed until after the final 6-hour post dose sample is collected…**	Clarify PK collection procedures.
11.1.2.2, Other Secondary Assessments	• OCA (~~and its conjugates~~) and C4 will be assayed	• OCA **(OCA, tauro-OCA, glyco-OCA, total OCA, OCA-glucuronide)** and C4 will be assayed **to determine bioanalytical concentrations. Additional analyses may include other conjugates or metabolites not yet identified**.	Clarify the analytes to be measured for the PK analyses.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
11.1.2.4, Potential Clinical Outcome Events	(Insertion)	**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 13.4.**	Revised to clarify that potential clinical outcome events meeting the criteria of a SUSAR will not be reported to regulatory authorities expeditiously.

12.1.4.2 Reporting of Serious Adverse Event	In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the ~~medical monitor.~~ All SAEs ~~occurring while subjects are receiving investigational product or are on an investigational product holiday (including Potential Clinical Outcome Events that qualify as serious)~~ must be reported to the ~~medical monitor immediately (ie, within 24 hours) after the Investigator identifies the SAE~~. SAEs are reported by entering the SAE data into the ~~electronic data capture (EDC) system~~. Entering the SAE data into the EDC system will automatically notify the ~~medical monitor~~ of the event. In the event that the EDC system is inaccessible, an SAE may be reported by ~~telephone or fax~~ using a paper SAE Report form. 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: ~~subject~~ number and ~~initials, a description of the event~~, at least **one** criterion classifying the event as serious and the name and title of the reporting individual. ~~Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting~~ to regulatory authorities by the Sponsor or designee(s). ~~Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the medical monitor. Any supporting source documentation should be faxed to~~	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 be reported by: • **E-mail to the SAE email address: sae@interceptpharma.com** • **Fax** using a paper SAE **report** form: **+1 800 497 8521** • **Telephone: +1 858 964 1571** 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: • **Subject** 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 Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) **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**	Updated guidance for reporting SAEs.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
	~~+1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible~~. 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. ~~A SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).~~ The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) ~~safety reports (SUSARs)~~ that occur during the study within the time frames required by each regulatory agency. ~~The Investigator is responsible for submitting information on IND safety reports/SUSARs received from the Sponsor or Sponsor designee to her/his local EC/IRB. Documentation of the submissions to IRBs and health authorities must be retained in the appropriate study file(s).~~ ~~Potential Clinical Outcome Events (Appendix A) as well as Anticipated Events (Appendix B) will not undergo expeditious reporting to regulatory authorities~~	**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 +1 800 497 8521 or emailed to sae@interceptpharma.com as soon as possible.** **The Investigator is responsible for submitting information on IND 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 IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND 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 12.1.5.**	

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
Section 12.1.5, Suspected Liver-related Clinical Outcome Events	Clinical Outcome Events ~~(Appendix A) as well as Anticipated Events (Appendix B) will not undergo~~ expeditous reporting.	**12.1.5 Suspected Liver-Related Clinical Outcome Events** **Specified liver-related clinical outcome events may, by definition (see Section 12.1.1.2) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 12.1.4.2). 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.** **Given that the liver-related clinical outcome events could also meet the criteria of a SUSAR, please refer to Section 11.1.2.4.** **The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial and peritonitis (preferred term: peritonitis bacterial).**	Updated section to account for events related to hepatic impairment**.**

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
13.2.4, Cardiovascular Adjudication Committee	13.2.3 (…) In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study ~~and will be described separately~~.	**New Section: Cardiovascular Adjudication Committee** In addition to potential clinical endpoint events, cardiovascular events will be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study. **Adjudicated cardiovascular events include core major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes may be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (see Section 13.4).**	Committee added to assess cardiovascular events in subjects during the study.

13.4, Adjudication Committee	All ~~potential endpoint events~~ will be reviewed by ~~an~~ adjudication committee before inclusion in the any analysis. The ~~adjudication of potential clinical endpoint~~ events will include, ~~but is not limited to: available hospital reports, histology, discharge summaries, and death certificates. The assessment of events will be conducted in compliance with the protocol, study-specific procedures, manuals, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents. A separate adjudication committee charter will document the entire data flow and process from committee membership~~, the reporting of events by the study site, ~~reporting~~ of the ~~final assessment,~~ supply of source documentation to the committee, ~~the~~ review of the events by the committee, and the working procedures of the committee. The adjudication committee members will be independent hepatologists not involved in the study as investigators, DSMC members, or consultants. All adjudication committee members ~~will remain blinded to treatment group throughout the study~~. ~~In addition to potential clinical endpoint events, cardiovascular events will also be adjudicated. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study and will be described separately.~~	All **suspected liver-related clinical outcomes, 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 subject treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific**	Committees added to assess liver impairment in subjects during the study.

Section	Original Text (Amendment 1.1, 12 November 2015)	Revised Text (Version 3, 07 September 2016)	Justification for Change
		procedures, manuals, good clinical practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.	
Appendix A, Modified Dosing Regimen for Subjects with Child-Pugh B/C Hepatic Impairment	(Insertion)	New**: APPENDIX A. MODIFIED DOSING REGIMEN FOR SUBJECTS WITH CHILD-PUGH B/C HEPATIC IMPAIRMENT**	Added section to describe changes in dosing and titration for subjects assessed as cirrhotic Child-Pugh B or Child-Pugh C.
Appendix B, LIST OF STUDY 747-302 OUTCOME EVENTS	Was Appendix A	Now Appendix B	The hepatic dosing appendix became Appendix B
Appendix C	~~LIST OF STUDY 747-302 ANTICIPATED EVENTS~~	Deleted	Replaced by Appendix B, more comprehensive description of the outcome events.

APPENDIX G. SUMMARY OF CHANGES: PROTOCOL VERSION 3 TO PROTOCOL VERSION 3.1 (DATED 23 DEC 2016)

Please note that Protocol 747-302 Version 3.1 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. This summary of changes is provided for completeness. A full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided in Appendix I.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the expansion of the spectrum of stages of PBC disease, the addition of progression to cirrhosis as a secondary endpoint, and the addition of two interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

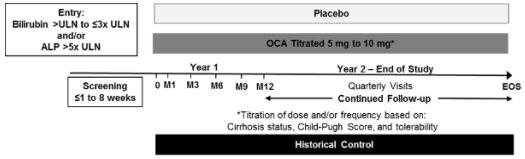
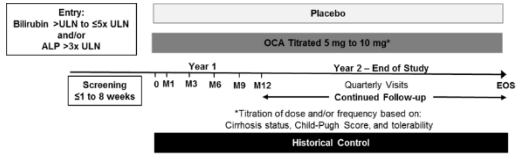
The following table includes revisions that were made to Protocol Version 3.1 with an associated reason or justification for the change. Rationales (Justifications for Change) that impact multiple sections are provided below and referenced in the table with the appropriate rationale number.

1. The phase of the study has been changed from '3b' to '4' to reflect that this is a post-marketing study.
2. The term 'primary biliary cirrhosis' has been changed to 'primary biliary cholangitis' throughout the document to reflect recent changes in nomenclature for PBC.
3. The increase in number of required events from 121 to 127 is due to the addition of two interim analyses (IA), which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy or futility) of the study. One IA will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). Inclusion of patients with earlier stage disease will also increase the time to event requiring more events in order to keep follow-up to approximately 6 years.
4. The first-year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by two years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.
5. 'Encephalopathy' has been modified to 'Hepatic Encephalopathy' to clarify that the relevant clinical outcome endpoint should be related to hepatic disease.

6. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of Hepatocellular Carcinoma.
7. **Broadening the Spectrum of Disease:** Lowering the minimum allowable baseline ALP to 3x ULN and raising the maximum allowable baseline total bilirubin to 5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the phase 3 protocol 747-301.
8. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
9. The increase in enrollment from 350 to 428 is due in part to the increased number of events, and in part due to the change in the estimated Placebo baseline hazard rate which resulted from changing the lower limit of ALP from 5× ULN to 3× ULN in the enrollment criteria #2.
10. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential non-invasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of 302.

The text deleted from Protocol Version 3 is crossed out while revised text in Version 3.1 is indicated in bold font in the table below. Minor/editorial changes and non-substantial changes are not listed individually in the summary table below.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	**Or if Not Available:** Contact: PPD **MD, PhD Medical Director, Clinical Research,** Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD	Back-up medical monitor responsibilities were transferred to PPD
Synopsis, Studied Period (years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	~~3b~~	**4**	Rationale 1
Synopsis, Objectives, Primary, Statistical	• Encephalopathy (as defined by a West Haven score of ≥2) • Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5 Rationale 6

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis		• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities **unless confirmed by biopsy**	
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***Insertion*** To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects	**To assess the effect of OCA compared to placebo on progression to cirrhosis** To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 6
Synopsis, Methodology: Schematic Diagram Section 7.1.1 Study Design Diagram, Figure 1	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.	 Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. • Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability and biochemical response of the product.	Rationale 7 Rationale 8

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (planned)	Approximately ~~350~~ subjects	Approximately **428** subjects	Rationale 9
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ≤~~3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 7
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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:	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below:	Standardizing language across protocols; removing double-barrier terminology

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 3.1, 23 December 2016)</th><th>Justification for Change</th></tr>
<tr><td></td><td>• ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~
• Intrauterine device (IUD)~~; 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 subject</td><td>• Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide
• Intrauterine device (IUD)
• Vasectomy (partner)
• Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
• Abstinence, if in line with the preferred and usual lifestyle of the subject</td><td></td></tr>
<tr><td>Synopsis, Exclusion Criteria
Section 8.3 Subject Exclusion Criteria</td><td>3. Mean total bilirubin >~~3~~x ULN</td><td>Mean total bilirubin >**5**x ULN</td><td>Rationale 7</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities</td></tr><tr><th>Secondary Objectives</th><th></th></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Hepatic encephalopathy (as defined by a West Haven score of ≥2)
• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities already confirmed by biopsy</td></tr><tr><th>Secondary Objectives</th><th></th></tr></table></td><td>Rationale 5

Rationale 10</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		Progression to cirrhosis — **Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated**	
Synopsis, Statistical Methods Analysis Populations	The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.	Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population.
Synopsis, Statistical Methods, Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints.	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints.	
Synopsis, Statistical Methods, Other Efficacy Analyses Section 13.1.5 Additional	***Insertion***	**Progression to cirrhosis will be assessed in the subset of subjects considered non-cirrhotic at baseline using available medical history, clinical, and laboratory assessments as well as baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be**	Rationale 10

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Secondary Efficacy Analyses		**considered non cirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the trial in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of non-cirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.** **Analyses for the histological assessment conducted as part of the biopsy sub-study are defined in Appendix C.**	
Synopsis, Statistical Methods, Safety Analyses	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will ~~compare OCA and placebo using~~ the Safety Population.	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results will **be summarized by treatment group for** the Safety Population.	Clarification of summary analyses
Synopsis, Statistical Methods, Sample Size Justification	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes.	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up • ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **subject** accrual and 6 years of follow up • **Two interim analyses and one final analysis are planned** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to clinical outcomes. In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	Rationale 4 Rationale 3
Section 5.6 Summary of Known Potential Risks with OCA	~~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).~~	**An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg and in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies.**	Language has been updated to reflect Sponsor standards

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	Insertion	**Refer to the IB for additional information regarding the known potential risks with the investigational product.**	
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3). The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5**× ULN or ALP >**3**× ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**….based on tolerability **and biochemical response** (see Section 7.3) The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 1 Rationale 9 Clarification Rationale 7 Rationale 3
Section 7.1.2 Schedule of Study Procedures, Table 1	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration** • **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	[j] Transient elastography (TE) will be conducted at selected study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments at Day 0 and Month 12)
	[l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	[m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds**: unless HCC has already confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met	Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis. Rationale 8
	[o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. …	[p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. …	Clarification
	[u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a baseline (e.g. Day 0) genetic sample is not obtained, subsequent genetic samples are not**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		required to be collected during the course of the study.	
Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions*** [i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~ Not required if done within ~~6~~ months of visit. ***Insertion*** (subsequent footnotes are renumbered accordingly) [j] Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up** [i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. Not required if done within **3** months of visit [j] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Not required if done within 6 months of visit.** [k] Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: **unless HCC has already been confirmed by biopsy,** a second confirmatory image (eg, MRI) should be obtained to confirm if a study endpoint has been met.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments) Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis.
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	are expected to have a minimum follow-up time of approximately 6 years.	are expected to have a minimum follow-up time of approximately 6 years.	
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study.	Rationale 9
Section 7.3 Planned Dosing Regimen	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score ***Footnotes were re-ordered*** [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin >ULN**. Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Rationale 8
Section 7.4 Dose Titration Criteria	***Insertion***	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total**	Added language to clarify titrations (up or down)

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		bilirubin to within normal limits, or 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 for each dosing regimen as defined in Section 7.3.	
Section 8.4.1.1 Severe Drug-Induced Liver Injury	***Insertion***	**If a subject develops signs and symptoms of a severe drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline, but the subject should continue with the study visit schedule. Subjects who develop significant drug-induced liver injury which is considered 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, evidence of 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.** **Severe drug induced-liver injury that is not considered related to investigational product must be discussed with the Sponsor before investigational product is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed**	Added guidelines for subjects who develop severe Drug-Induced Liver Injury

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time. **All suspected drug-related hepatic injury events will be adjudicated by the Hepatic Safety Committee (see Section 13.4).**	
Section 8.4.1.2 Liver Transplantation	***Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product***	**8.4.1.2 Liver Transplantation** **Subjects must discontinue investigational product after undergoing liver transplantation surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection.**	The relocation of this statement from within Section 8.4.2 to 8.4.1.2 clarifies directions to discontinue subjects who undergo a liver transplant from investigational product but not study visits
Section 8.4.2 Reasons for Mandatory Interruption of Investigational Product	***Insertion/Reorganization***	**8.4.2 Reasons for Mandatory Interruption of Investigational Product** **Prior to re-starting investigational product after a prolonged interruption, the subject must be re-consented and new baseline visit procedures must be performed if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.**	This clarifies what should be done when a subject experiences a prolonged interruption in investigational product such as in the event of pregnancy
Section 8.4.2.1 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product	**8.4.2.1 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product	Language simplified and aligned with Sponsor standards

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~	**immediately,** but should continue with the study visit schedule. **As described in Section 12.1.9** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.9). New baseline procedures should include pregnancy testing.**	
Section 8.4.3 Other Reasons for Discontinuation of Study of Investigational Product	8.4.2 Other Reasons for Discontinuation of Study of Investigational Product Subjects ~~that~~ discontinue investigational product are expected to continue in the study until the end of the study~~, and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ or at the discretion of the Sponsor. ~~If a~~ a subject ~~reaches an event,~~ he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who ~~choose to~~ discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and~~	**8.4.3** Other Reasons for Discontinuation of Study of Investigational Product 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. **With the exception of liver transplant, if** a subject **experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor):	Discontinuation of investigational product language updated to clarify the process that is to be followed after discontinuation and instruct subjects to continue regular visit schedule.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~the study will only terminate~~ (or at the discretion of the Sponsor): – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or cardiovascular events~~. ~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.~~	– 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), liver-related clinical outcomes, and drug-related hepatic injury events.** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** To determine which dosing regimen subjects should follow, the presence or absence of 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~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** To determine which dosing regimen subjects should follow, the presence or absence of cirrhosis should be assessed by the Investigator at Screening Visit 1. Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as non-cirrhotic at baseline per the criteria listed in Section 9.7.3.1 exhibits any of those same criteria (excluding biopsy results consistent with PBC Stage 4), the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites**	Provides detail around the assessment of Progression to Cirrhosis as a secondary endpoint

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		participating in the paired biopsy sub-study (see Appendix C**) must confirm progression to cirrhosis by biopsy. All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	
Section 9.7.6 Screening Procedures	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN).	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5**× ULN and/or an ALP >**3**× ULN).	Reflects new inclusion criteria
Section 9.7.7 Day 0 Procedures	• Perform transient elastography ~~(TE; at selected study sites, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	• Perform transient elastography **at all study sites with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required.	Clarifies use of TE and modifies the time during which an historic TE report remains valid
Section 9.7.8 Month 1 Procedures Section 9.7.10 Post-titration visit Procedures	***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit requirements:	• **Perform a physical examination.** – In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit **laboratory** requirements:	Physical examinations 1 month after initiating dosing with investigational product will enhance safety monitoring Returning to the site for monthly laboratory assessments can present a significant burden on subjects, thus alternatives are provided for collecting lab samples; with the addition of the physical exam as well the requirement for these exams is provided in the context of the alternatives for laboratory specimen collection

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion***	• **Perform a physical examination** • **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).**	TE assessment has been added as biannual assessment at all study sites with access to Fibroscan® TE device Hepatic ultrasound should be performed biannually per AASLD and EASL guidelines for subjects with PBC
Section 11.1.2 Secondary Assessments	***Insertion***	• **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.** • **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (see Appendix C)**	Rationale
Section 11.1.2.4 Potential Clinical Outcome Events	The events listed in ~~Appendix A~~ will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	The events listed in **Section 12.1.5** will be initially assessed by the Investigator to determine if they are Potential Clinical Outcome Events.	Appendix referencing clinical outcomes events was removed due to redundancy
Section 12.1.4.2 Reporting of Serious Adverse Events	***Insertion***	**Redacted medical record source documentation will be requested for all SAEs and emergency room visits.**	Added sentence regarding redacted medical records to align with Sponsor safety standards
Section 12.1.5 Suspected Liver-Related Clinical Outcome Events	~~For~~ liver-related clinical outcome events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, ~~please refer to Section 11.1.2.4.~~	**Given that the** liver-related 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 liver-related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes**	Updated to align with modified standard safety procedures and Sponsor standard language

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), and spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).	**endpoint. These events will be selected as a "study event" on the Adverse Event CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4.** The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).**	
Section 12.1.7 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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours).	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 12.1.4.2.	Updated to align with modified safety procedures and Sponsor standard language
Section 12.1.8 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. Note that longer follow-up can sometimes reveal an off-drug repetition**	Updated to align with modified standard safety procedures and Sponsor standard language

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.	
Section 12.1.9 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~~ investigational product and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing~~ or ~~emailing~~ to ~~the Sponsor at~~ +1 800 497 8521 or sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use of investigational product.~~ The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum β hCG test (see~~ Section 8.4.1~~).~~	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 8.4.2.1) 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** sae@interceptpharma.com **or faxed to** +1 800 497 8521. **The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.** The subject may **re-start** 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 subject must have a negative pregnancy test before restarting investigational product. If a subject'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**	Updated to align with modified standard safety procedures and Sponsor standard language

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 3.1, 23 December 2016)</th><th>Justification for Change</th></tr>
<tr><td></td><td></td><td>reporting procedures described in Section 12.1.4 must also be followed.</td><td></td></tr>
<tr><td>Table 10 List of Laboratory Analytes</td><td><table><tr><td>~~Measurement of Liver Fibrosis~~</td><td>~~Fibroscan~~</td></tr><tr><td>~~Bone Density Assessment~~</td><td>~~DEXA~~</td></tr><tr><td>Other</td><td>Insertion</td></tr></table></td><td>Deletion<table><tr><td>Other</td><td>OCA-glucuronide</td></tr></table></td><td>Measurements of liver fibrosis are captured in a different section

OCA-glucuronide was listed in the text but missing from the table</td></tr>
<tr><td>Section 13.1.1 Analysis Populations</td><td>• ~~The Randomized Population will include all randomized subjects~~</td><td>Deletion</td><td></td></tr>
<tr><td>Section 13.1.2.1 Sample Size Monitoring</td><td>9.1.2.1 Sample Size ~~Re-Estimation Plan~~
~~Therefore, starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups.
~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative~~</td><td>9.1.2.1 Sample Size Monitoring
Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of 127 adjudicated events for the final analysis in the combined groups.
Deletion</td><td></td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~primary efficacy analysis is specified is Section 13.1.9.~~ ~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~		
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between the effect of OCA on ALP and bilirubin and the clinical benefit of OCA will be evaluated by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This analysis will be based on the ITT population.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
13.1.8 Supportive Analysis	***Insertion***	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct based on the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised primary efficacy analysis. This analysis would compare all subjects in the OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section 13.1.2.1), using**	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		similar statistical methodology as specified above. **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	Sponsor has received agreement from regulatory authorities.
Section 13.1.9 Alternative Primary Analysis	~~13.1.9 Alternative Primary Analysis~~ ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new primary efficacy analysis will become the comparison of all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause) (see Section **13.1.2.1**). Similar statistical methodology as specified above in Section **13.1.8** for supportive analyses will be utilized.~~ ~~The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section **13.1.8** will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~	***Deletion***	As a placebo-controlled study, the alternative primary analysis section has been removed. Upon review of blinded data, the DMC may recommend changes to study conduct. However, such recommendations will not be implemented unless the Sponsor has received agreement from regulatory authorities

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
	~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs and/or loss of patients to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy or futility) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.**	Explanation of the type of review that will be ongoing by the DMC during study conduct.
Section 19 List of References	***Insertion***	**Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential**	Additional relevant references were added.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
		Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.	
Appendix B List of Study 747-302 Outcome Events	~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~	**Deleted**	Redundant; Information is contained within the protocol
Appendix C Biopsy Sub-Study of Protocol 747.302: A Phase 4, Double-Blind, Randomized, Placebo-Controlled,	***Insertion***	**See Appendix C**	The purpose of this sub-study is to assess the effect of OCA versus placebo on the histological severity of disease (fibrosis/cirrhosis) in subjects with PBC. In addition, this sub-study will demonstrate the relationship between

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 3.1, 23 December 2016)	Justification for Change
Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in subjects with Primary Biliary Cholangitis			histological changes and clinical, laboratory, and non-invasive measures indicative of progression to cirrhosis in patients with PBC.

APPENDIX H. SUMMARY OF CHANGES: PROTOCOL VERSION 3.1 TO PROTOCOL VERSION 4 (DATED 10 MAY 2017)

Please note that Protocol 747-302 Version 3.1 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. A full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided in Appendix I.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 Version 3.1 include:

- Hepatocellular carcinoma (HCC) has been redefined as a secondary endpoint;
- Following the broadening of the spectrum of disease, a commitment to enroll a minimum of 30% of subjects with abnormal bilirubin has been added to the protocol;
- Clarifications have been incorporated throughout the protocol based on the addition of a biopsy substudy in Addendum 2;
- Statistical language has been modified and added to clarify statistical assumptions and analyses including the addition of a Per Protocol (PP) Population;
- Background rationale has been updated to reflect the current approval status of Ocaliva; and
- Safety language has been updated throughout the protocol to reflect the updating of Sponsor standards.

Minor revisions include editorial changes such as removal of hyphens and capitalization of words. Minor revisions may be included in the following table when they are also part of major revisions; however, most minor/editorial changes and nonsubstantial changes are not listed individually.

The text deleted from Protocol Version 3.1 is crossed out while revised text in Version 4 is indicated in bold font in the table below.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Study Personnel Contact Information	~~**Or if Not Available:**~~ ~~Contact:~~ PPD ~~MD, PhD Medical Director, Clinical Research,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~Mobile:~~ PPD ~~(Pacific time zone)~~ ~~Email:~~ PPD PPD ~~**Clinical Operations and Project Management**~~ ~~Contact:~~ PPD PPD ~~Clinical Operations,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~(Pacific time zone)~~ ~~Mobile:~~ ~~Fax:~~ PPD ~~Email:~~ PPD PPD		Updating emergency medical monitor contact information. The contact information for clinical operations and project management personnel is no longer required in the protocol per Sponsor's procedures.
Synopsis, Objectives, Primary, Statistical Methods – Efficacy Analyses	To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary ~~cirrhosis~~ (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:	To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with primary biliary **cholangitis** (PBC) as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint:	Editorial correction HCC has been redefined as a secondary endpoint instead of a component of the primary

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy~~		composite-event endpoint per Regulatory Authority request.
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	***In Section 6.2*** To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above ~~and also to include liver related death~~. To ~~characterize~~ the effect of OCA compared to placebo on progression to cirrhosis. To ~~assess~~ the PK of OCA and its conjugates in a subset of subjects.	**To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).** To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above. **To assess the effect of OCA compared to placebo on time to occurrence of liver-related death.** To **assess** the effect of OCA compared to placebo on progression to cirrhosis. To **characterize** the PK of OCA and its conjugates in a subset of subjects.	HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request. Editorial change Editorial change Editorial change
Synopsis, Methodology Section 7.1, Overall Study Design.		**A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.**	To ensure enrollment of an adequate number of subjects with abnormal total bilirubin.

<table>
<tr><th>Section</th><th>Original Text
(Amendment 3.1, 21 December 2016)</th><th>Revised Text
(Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td>Section 7.1.1
Study Design Diagram,
Fig 1 (Footnote)</td><td>Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response.</td><td>Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN).</td><td>Clarification of biochemical response</td></tr>
<tr><td>Synopsis, Number of Subjects (Planned)

Section 7.2
Number of Subjects</td><td>Insertion in both, Synopsis and Section 7.2

Change in Synopsis section

Approximately 428 subjects</td><td>In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned.

Approximately 428 subjects are planned to be enrolled in the study.</td><td>Language added to allow for continued enrollment into the biopsy substudy; additional subjects are not anticipated to prolong the duration of the study.</td></tr>
<tr><td>Synopsis, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td></td><td>• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy.~~</td></tr><tr><td>Secondary Objectives</td><td></td></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td></td><td></td></tr><tr><td>Secondary Objectives</td><td></td></tr><tr><td>HCC</td><td>Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy</td></tr></table></td><td>HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.</td></tr>
<tr><td>Synopsis, Statistical Methods
Analysis Populations</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBC Historical Control.</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP), Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBC Historical Control.</td><td>The randomized population is included within the Safety population.
The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.</td></tr>
</table>

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Primary Efficacy Endpoint Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	~~• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~ ***Section 13.1.3*** ~~• Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities unless confirmed by biopsy~~ The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population.	***Section 13.1.3*** The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population.	HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request. Editorial change
Synopsis, Statistical Methods, Primary Efficacy Analysis Section 13.1.3 Primary Efficacy Analysis	***Insertion***	**The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses Section 13.1.4 Secondary Efficacy Analysis	***Insertion*** ***Section 13.1.4*** The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in the ITT population with respect to the key secondary efficacy endpoints.	**The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.** ***Section 13.1.4*** The key secondary efficacy analyses will compare OCA to placebo in the ITT population with respect to the key secondary efficacy endpoints.	The PP population will be used to conduct sensitivity analyses for primary and key efficacy endpoints. Editorial change

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Additional Secondary Efficacy Analyses	~~Other~~ Efficacy Analyses The following secondary efficacy analyses will compare OCA ~~to~~ placebo ~~on time to the following events~~: • Each component of the primary efficacy endpoint (except MELD score ≥15 which is listed above) • Development of varix/varices • Liver-related death • Liver-related death or liver transplant Liver-related death, liver transplant, or MELD score ≥15	**Additional Secondary** Efficacy Analyses The following **time-to-event** secondary efficacy analyses will compare OCA versus placebo using **the ITT population**: • **Time to e**ach component of the primary efficacy endpoint (except MELD score ≥15 which is listed above) • **Time to d**evelopment of varix/varices • **Progression to cirrhosis** • **Time to occurrence of HCC** • **Time to l**iver-related death • **Time to l**iver-related death or liver transplant **Time to l**iver-related death or liver transplant, or MELD score ≥15	Editorial Change Progression to cirrhosis added as secondary endpoint in Version 3.1. HCC has been redefined as a secondary endpoint instead of a component of the primary composite event endpoint per Regulatory Authority request.
Synopsis, Statistical Methods, Additional Secondary Efficacy Analyses Section 13.1.5 Additional Secondary Efficacy Analyses	***Insertion*** Analyses for the histological assessment conducted as part of the biopsy substudy are defined in ~~Appendix C~~.	**For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy.** Analyses for the histological assessment conducted as part of the biopsy substudy are defined in **Addendum 2.**	Provides further details of progression to cirrhosis as outlined in the biopsy substudy defined in Addendum 2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	***Insertion*** The following assumptions were used in sample size calculations: • Two interim analyses and one final analysis are planned. ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to ~~clinical~~ outcomes.	**The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN.** The following assumptions were used in sample size calculations: • Two interim analyses and one final analysis are planned. **The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.** • **A dropout rate of 10% is assumed.** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of 127 events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to **liver-related** outcomes**, including all-cause mortality**.	Incorporation of the broadened spectrum of disease into the sample size justification. Clarification of interim analyses. Clarification of the assumed dropout rate. Clarification of outcomes being assessed in power calculations.
Section 5.1 Overview of PBC and OCA	5.1. Overview of Primary Biliary ~~Cirrhosis~~ and Obeticholic Acid Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis~~)~~ 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	5.1. Overview of Primary Biliary **Cholangitis** and Obeticholic Acid 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	Updating language to include accelerated and conditional approvals of OCA in the US and EU.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	necessitates liver transplantation or results in death. Ursodeoxycholic acid (UDCA), a physiological constituent of human ~~bile , is currently the only treatment approved for PBC~~ (Lindor 2009). While UDCA therapy ~~has~~ a marked effect on the treatment of PBC, up to 50% of patients ~~show~~ a suboptimal response or no response to UDCA. Such patients ~~are~~ at significantly increased risk of a poor clinical outcome due to PBC disease progression~~. There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]).~~ Obeticholic acid (OCA) ~~is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.~~ ~~OCA is a modified bile acid and~~ farnesoid X receptor (FXR) agonist ~~that is~~ derived from the primary human bile acid chenodeoxycholic acid (CDCA~~). OCA is currently being developed in the United States (~~US~~) and Europe for the treatment of PBC and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States~~ Food and Drug Administration	necessitates liver transplantation or results in death. **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**), 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 (Pellicciari 2002). 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.	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	(FDA) ~~has~~ granted accelerated approval for Ocaliva ~~for the treatment of PBC.~~ Ocaliva ~~is not yet approved outside the United States for use in any~~ indication.		
Section 5.4 Overview of PBC and OCA	As of 31 Jan ~~2016~~, approximately ~~1726~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ subjects had PBC, ~~330~~ subjects had NASH, 41 subjects had diabetes mellitus/~~non-alcoholic~~ fatty liver disease ~~(NAFLD)~~, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~20~~ subjects had primary sclerosing cholangitis (~~PSC~~).	As of 31 Jan **2017**, approximately **2186** subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** subjects had PBC, **686** subjects had NASH, 41 subjects had diabetes mellitus/**nonalcoholic** fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **52** subjects had primary sclerosing cholangitis, **and 5 subjects had biliary atresia.** **----------** **[1]Includes estimated numbers from ongoing blinded studies.**	Language updated to include data from current IB.
Section 5.5.2.1 Rationale for OCA Dose	The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; ***Insertion*** Based on these data, ~~the indicated commercial doses of~~ OCA for the treatment of patients with PBC are 5 mg and 10 mg. ~~As such,~~ Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.	The Phase 3 PBC study **(Study 747-301)** subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; **Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus.** Based on these data, the **approved dosing regimens for** OCA for the treatment of patients with PBC are 5 mg and 10 mg. Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose **for at least 3 months**, increasing to 10 mg OCA, if tolerated.	Provides rationale for the dosing in alignment with commercial labeling.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 5.6 Summary of Known Potential Risks with OCA	~~An increase in liver enzymes and~~ hepatic ~~AEs, including jaundice,~~ were observed in ~~subjects with liver disease at OCA doses between 10 mg and 50 mg and in~~ healthy ~~subjects who were~~ treated ~~at doses ≥100 mg in Phase 1,~~ multiple-~~dose studies~~. These findings were seen more frequently with doses ~~above~~ 10 mg OCA.	**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)**. 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).**	Language has been updated to reflect Sponsor standards.
Section 7.1.2 Schedule of Study Procedures, Table 1	[a] All subjects will have the chemistry panel retested to ensure subjects have two ALP and bilirubin assessments 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. [l] Endoscopy will be conducted at ~~selected~~ study sites where the device is available. [m] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: Unless HCC has already confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met~~.	[a] All subjects will have the chemistry panel retested to ensure subjects have **at least** two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. **Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility.** [l] Endoscopy will be conducted at **all** study sites where the device is available**.** [m] 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**.	Editorial changes
Section 7.1.2 Schedule of Study Procedures, Table 2	[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available. ~~Not required if done within 3 months of visit.~~	[i] Transient elastography (TE) will be conducted at 6-month intervals at all study sites where the Fibroscan® TE device is available.	Editorial changes

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. ~~Not required if done within 6 months of visit~~. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met.~~	[j] DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, postday 0) ultrasounds: unless HCC has already been confirmed by biopsy, a second confirmatory image (eg, MRI) should be obtained to confirm **suspected HCC**.	
Section 7.4 Dose Titration Criteria	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.	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, **biochemical response**, and clinical judgment. **Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).**	Editorial changes
Section 7.4.1 Pre-Titration Tolerability Assessment Requirements	• There must be no clinically significant increase (as determined by the ~~i~~nvestigator) in the subject's liver function tests. ~~Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19 should be implemented, as required.~~	• There must be no clinically significant increase (as determined by the **I**nvestigator) in the subject's liver function tests.	Clarification
Section 7.4.2	***The text in this section is moved to Section 8.4.***		To avoid redundancy

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Safety Criteria for Adjustment or Stopping Doses			
Section 8.4 Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	**[*Moved from Section 7.4.2 of Version 3*]** Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be **adjusted back** to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved. Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an **outcome** event, he or she should continue the regular visit schedule and continue taking investigational product as long as the **subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the** Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Clarification
Section 8.4.1.1 Reasons for Additional Monitoring Related to Liver Chemistries	***Modification of 8.4.3.1 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~~	**Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total**	Clarified guidelines for subjects who develop elevations in liver chemistries. Language related to interruption of investigational product is now located in Section 8.4.1.2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~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.~~	**bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored.**	
Section 8.4.1.2 Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	***Insertion***	**Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3x baseline (and >ULN)** • **Total bilirubin >2x 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 AE information should also be collected and the subject 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**	Clarified guidelines for subjects who develop elevations in liver chemistries.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		medications should be identified and discontinued if advisable. **If symptoms persist or repeat testing shows AST or ALT >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 investigative product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject 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**	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		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 subject 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.** Subjects who develop **evidence of severe** drug-induced liver injury, which 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. **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 subjects 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**	

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Section 8.4.1.1: Subjects who develop ~~significant~~ drug-induced liver injury which is ~~considered~~ 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, ~~evidence of~~ functional hepatic impairment as indicated by rising bilirubin or INR that cannot be explained by progression of disease. ***Insertion***	**appropriate for the subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.** **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 13.4).**	
Section 8.4.1.3 Pregnancy	**8.4.2.1 Pregnancy** As described in Section ~~12.1.9~~ pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 ~~12.1.9~~). ~~New baseline procedures should include pregnancy testing~~.	**8.4.1.3 Pregnancy** As described in Section **12.1.11** pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 **12.1.11**.	Revised section number.
Section 8.4.2.1 Liver Transplantation	**8.4.1.2 Liver Transplantation** Subjects must discontinue investigational product ~~after undergoing liver transplantation surgery.~~ Subjects should be encouraged to ~~continue study visits, despite stopping investigational product, for continued study data collection~~.	**8.4.2.1 Liver Transplantation** Subjects **who undergo a liver transplant during the course of the study** must discontinue investigational product **and discontinue the study visit schedule. However, these** subjects 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**.	Clarification on process for subjects who undergo a liver transplant.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 8.4.3 Other Reasons for Discontinuation of Study or Investigational Product	~~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. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18).~~ – Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess suspected major adverse cardiovascular events (MAC), liver-related clinical outcomes~~, and drug-related hepatic injury events~~.	– Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess suspected major adverse cardiovascular events (MACE) **and** liver-related clinical outcomes. – **Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.18).**	Clarification of process
Section 9.7.1 Visit Windows	Screening |	Screening | **See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.**	
Section 9.7.3.2 Progression to Cirrhosis	When a subject identified as ~~non-cirrhotic~~ at Baseline per the criteria listed in Section 9.7.3.1 exhibits any ~~of those~~ same criteria ~~(excluding biopsy results consistent with PBC Stage 4)~~, the	When a subject identified as **noncirrhotic** at Baseline per the criteria listed in Section 9.7.3.1 exhibits any **signs or symptoms associated with progression to cirrhosis, as defined by the** same	Details the assessment of progression to cirrhosis.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy unless not medically indicated. Sites participating in the paired biopsy ~~sub-study (see Appendix C)~~ must confirm progression to cirrhosis by biopsy.	criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis confirmed by biopsy **(centrally read)** unless not medically indicated. **Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis.** **Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.** Sites participating in the paired biopsy **substudy** must confirm progression to cirrhosis by biopsy **as per the information outlined in protocol Addendum 2.**	
Section 9.7.6 Screening Procedures	~~Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated~~ serum chemistry samples (at least 2 weeks apart) ~~to confirm~~ pretreatment ALP and total bilirubin ~~values~~: ***Insertion***	**Collection of 2 s**erum chemistry samples (**collected** at least 2 weeks apart**) during Screening is required for confirmation of the** pretreatment **serum chemistry values, including the** ALP and total bilirubin **used to determine eligibility**: • **When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Allows repeat assessments when baseline laboratory values are discrepant between Screening Visit 1 and Screening Visit 2.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	• …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (~~selected~~ study sites ~~only~~), ***Insertion***	• …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 **(at all** study sites **where the device is available**), **In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.**	
Section 9.7.8 Month 1 Procedures Section 9.7.10 1-Month Post-Titration visit Procedures	***Insertion (9.7.8)*** ***Insertion (9.7.10)***	– **A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed**. – **A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed**.	Clarification
Section 9.7.12 Month 9 Procedures Section 9.7.14 Month 12 Procedures Section 9.7.16 Month 16 Continued Follow-Up Procedures Section 9.7.17 Month 12 Follow-up Procedures Section 9.7.18 EOS/EOT	***Section 9.7.12, 9.7.14, 9.7.16, 9.7.17, and 9.7.18*** *…DEXA procedure to be done at* ~~selected~~ study sites ~~only~~, ***Section 9.7.14, and 9.7.17*** • Perform an endoscopy (at ~~selected~~ study sites, where available)	***Section 9.7.12, 9.7.14, 9.7.16, 9.7.17, and 9.7.18*** *…DEXA procedure to be done at* **all** study sites **where the device is available** ***Section 9.7.14, and 9.7.17*** • *Perform an endoscopy (at **all** study sites, where **device is** available)*	Clarification

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 9.7.18 EOS/EOT	If the subject reports having eaten within 8 hours, document accordingly in the source and CRF ~~and remind the subject that fasting is required prior to all study visits~~.	If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.	Clarification
Section 10.3 Investigational Product Storage	~~The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical study 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.**	Updating temperature excursions language per Sponsor stability studies.
Section 11.1.2 Secondary Assessments	***Insertion*** • Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in ~~Appendix C~~). • Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c reactive protein (CRP), tumor necrosis factor α (TNF-α), FGF 19, cytokeratin-18 (CK-18) and ELF, (and others as determined during the course of the study).	• **Individual components of the primary endpoint.** • Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in **Addendum 2**). • **HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.** • Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c reactive protein (CRP), tumor necrosis factor α (TNF-α), FGF 19, cytokeratin-18 (CK-18) ELF, and **Fibroscan** (and others as determined during the course of the study). • **Clinical outcomes, including individual component of the primary endpoint**	Clarified and re-ordered bullets for consistency throughout document. Addition of Addendum 2. Reflects addition of a biopsy substudy available to interested sites in Addendum 2.

<table>
<tr><th>Section</th><th>Original Text
(Amendment 3.1, 21 December 2016)</th><th>Revised Text
(Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td>• Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.</td><td>(where available), liver transplant, and death will be compared to historical controls.
• PK of OCA and its conjugates.
• Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.</td><td></td></tr>
<tr><td><u>Section 12.1.3</u>
Relationship of Adverse Events to Liver Biopsy</td><td>Insertion (new section)</td><td>The Investigator will document her/his opinion of relationship of an AE to liver biopsy using the criteria outlined in Table 9.
Table 9: Relationship of Adverse Events to Liver Biopsy<table><tr><th>Relationship</th><th>Description</th></tr><tr><td>Related</td><td>A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.</td></tr><tr><td>Not Related</td><td>Any event that does not meet the above criteria.</td></tr></table></td><td>Added with the addition of liver biopsies for the confirmation of progression to cirrhosis.</td></tr>
<tr><td><u>Section 12.1.5.2</u>
Reporting of Serious Adverse Events</td><td>~~•Telephone: +1 858 964 1571~~
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.</td><td>If an SAE is reported by email or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible.</td><td>Updated to align with modified standard safety procedures.</td></tr>
<tr><td><u>Section 12.1.6</u>
Suspected Liver-Related Clinical Outcome Events</td><td>Section 12.1.5
Given that the liver-related 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 liver-related clinical outcome events in order to retain the study</td><td>Section 12.1.6
Given that the liver-related clinical outcome events may also meet the criteria of a SUSAR, but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly, the Sponsor will not expeditiously report suspected</td><td>Updated to align with modified standard safety procedures and Sponsor standard language.</td></tr>
</table>

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	blind and preserve the integrity of the clinical outcomes endpoint. The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological progression to cirrhosis (preferred term: hepatic cirrhosis).	liver related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 **or oesophageal varices haemorrhage**), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites (preferred term: ascites), and histological **or clinical** progression to cirrhosis (preferred term: hepatic cirrhosis).	
Section 12.1.8 Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	***Insertion (new section)***	**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 12.1.5.2.** **SAEs that occur in subjects 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 12.1.5.2.**	Updated to align with modified safety procedures and Sponsor standard language.
Section 12.1.9 Notification of Poststudy SAEs	***Section 12.1.7*** All SAEs that occur within 30 days following the ~~cessation of investigational product~~, whether or	***Section 12.1.9*** All SAEs that occur within 30 days following **discontinuation from the study,** whether or not	Updated to align with modified safety procedures

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.~~4.~~2. ~~SAEs that occur more than 30 days after a subject has discontinued investigative product, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to investigational product, action taken with investigative product, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the Sponsor.~~	they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 12.1.**5**.2.	and Sponsor standard language.
Section 12.2.7 Laboratory Assessments	The list of laboratory analytes to be tested is shown in Table 1~~0~~.	The list of laboratory analytes to be tested is shown in Table 1**1**, **and the normal reference ranges for liver biochemistries are shown in Appendix C.**	Added per Regulatory Authority request.
Section 13 Statistical Methods	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to ~~study database lock~~, propensity score determination, and unblinding of the double-blind subject treatment assignments.	A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the **first interim analysis**, propensity score determination, and unblinding of the double-blind subject treatment assignments.	Reflects addition of interim analyses to the study protocol.
Section 13.1.1 Analysis Populations	***Insertion***	• **The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.**	The Per Protocol Population will be used to conduct sensitivity analyses for primary and key efficacy endpoints.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.1.1 Comparability of Historical Controls	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria ~~where possible~~.	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. **Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8**.	Clarifies the use of propensity scores in the assessment of the historical control population.
Section 13.1.5 Additional Secondary Efficacy Analyses	The following secondary efficacy analyses will compare ~~randomized~~ OCA ~~to randomized~~ placebo on using the ITT population:	The following **time-to-event** secondary efficacy analyses will compare OCA versus placebo using the ITT population: • **Progression to cirrhosis** • **Time to occurrence of HCC**	Editorial Change Progression to cirrhosis added as secondary endpoint in Version 3.1. HCC has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	The association between ~~the effect of OCA on~~ ALP and bilirubin and the clinical benefit of OCA will be evaluated ~~by estimating the proportion of net treatment effect on the primary composite endpoint that is explained by each biochemical marker. For each biochemical endpoint, this proportion will be estimated by applying the partial likelihood function to two Cox models that use the same failure time variable, as described in Lin 1997. This~~ analysis will be ~~based on~~ the ~~ITT population~~. Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.	The association between **biochemistry including** ALP and bilirubin **with clinical outcomes will be assessed** and the clinical benefit of OCA **using biochemistry as a surrogate endpoint** will be evaluated. **Detailed** analysis will be **described in** the **SAP**. Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of **OCA using biochemistry as a surrogate endpoint** for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.8 Supportive Analysis	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment. ~~Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a~~ full range of covariates across which the treatment and historical controls might differ. Only covariates and not outcome variables will be included in the propensity score estimation. ~~Therefore, there is no chance of biasing,~~ to avoid biased results that are in favor of one treatment.	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, **which serves as an external control for supportive analysis**. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment **between the treated subjects and the matched natural history subjects**. **A** full range of covariates across which the treatment and historical controls might differ **will be considered to mitigate potential bias**. Only covariates and not outcome variables will be included in the propensity score estimation **to avoid biased** results **that are** in favor of one treatment. **The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.** **A third-party statistician(s) will perform the propensity score modeling and matching. This**	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis. Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses. The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	
	The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes: • ~~Time to hepatocellular carcinoma~~		
Section 13.1.9 Handling of Dropouts or Missing Data	***Insertion***	**In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.**	Clarification of statistical analyses to address missing data.
Section 13.1.11 Examination of Subgroups	The primary and secondary efficacy endpoints will be analyzed for subject subgroups ~~(eg, age, sex, and race)~~ based on the ITT population. ***Insertion***	The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. **The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)** • **Early (normal albumin and normal bilirubin)**	Added per Regulatory Authority request.

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		• **Moderate (abnormal albumin or abnormal bilirubin)** • **Advanced (abnormal albumin and abnormal bilirubin)** **The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.** • **Monotherapy in patients who are intolerant or non-responsive to UDCA** • **Elderly patients** **Assuming a strong correlation between biochemistry and clinical outcomes using the total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement.** **Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
Section 13.1.12 Continuous Monitoring and Interim Analyses	Both interim analyses will be pre-specified and will occur after accrual of 50% and 75% of clinical outcome events, respectively. The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy ~~or futility~~) of the study beyond each interim analysis.	Both interim analyses will be pre-specified and will occur after accrual of 50% **(64 events)** and 75% **(96 events)** of clinical outcome events, respectively. The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation,	Added number of anticipated events. Clarification

Section	Original Text (Amendment 3.1, 21 December 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		modification, or cessation (for efficacy) of the study beyond each interim analysis	
Section 19 List of References	~~Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.~~ ***Insertion***	**Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Digestive and Liver Disease. 2015a;47(11):924-6.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6α-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-3572.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	Additional relevant references were added.
Appendix C Reference Laboratory Values from Central Laboratories	***Insertion (new appendix)*** ***Deletion:*** ***Appendix C in Version 3.1 has been deleted. It is now published as Protocol Addendum 2.***	***Appendix containing reference laboratory values from central laboratories added.***	Added per Regulatory Authority request.

APPENDIX I. SUMMARY OF CHANGES: PROTOCOL VERSION 3 TO PROTOCOL VERSION 4 (DATED 10 MAY 2017)

Please note that Protocol 747-302 Version 3.1 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. Therefore, a full accounting of the changes from Protocol Version 3 to Protocol Version 4 is provided below.

Rationale and Summary of Changes

Major revisions to Protocol 747-302 include the modification of inclusion/exclusion criteria to expand the PBC disease spectrum, the addition of progression to cirrhosis as a secondary endpoint, and the addition of 2 interim analyses. Additional revisions include an increase in subject number and the number of required clinical outcome events, a change in the study phase, an update to the nomenclature for PBC, and various clarifications within the protocol.

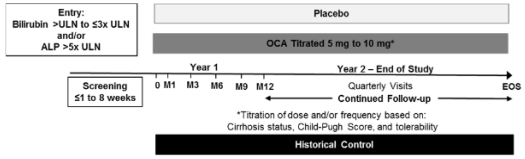
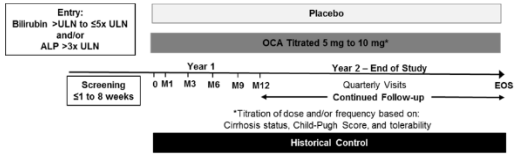
The text deleted from Protocol Version 3 is crossed out while revised text in Version 4 is indicated in bold font. Minor/editorial changes and non-substantial changes are not listed individually. For efficiency, rationales that impact multiple sections are provided below and referenced in the table with the corresponding rationale number.

1. **The phase of the study has been changed from "3b" to "4"** to reflect that this is a post-marketing study. Protocol 747-302 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC, ie, in the US and the EU. In all other regions, this study is considered Phase 3b. In May 2016, the FDA granted accelerated approval for OCA (Ocaliva) for the treatment of PBC. In December 2016, Ocaliva received Conditional Approval from the European Medicines Agency's Committee for Medicinal Products for Human Use.
2. **The term "primary biliary cirrhosis"** has been changed to "primary biliary cholangitis" to reflect recent changes in the nomenclature for PBC.
3. **The number of required adjudicated events for the final analysis has increased** from 121 to 127 due to the addition of two interim analyses, which will allow an independent DMC to recommend continuation, modification, or cessation (for efficacy) of the study. One interim analysis will occur at 50% information (after 64 events occur) and one at 75% information (after 96 events occur). In addition, inclusion of PBC subjects with earlier stage disease will increase the time to event, thereby requiring more events to maintain follow-up to approximately 6 years.
4. The first-year study enrollment rate was lower than projected due to slower-than-anticipated activation of sites and required a re-estimation of the accrual duration. Using observed accrual rates, the accrual duration was extended by 2 years. The follow-up period was maintained at 6 years, thereby leading to a total trial duration of 10 years.

5. "**Encephalopathy"** has been modified to "Hepatic Encephalopathy" to clarify that the relevant Clinical Outcome Event should be related to hepatic disease.
6. **Hepatocellular carcinoma** (HCC) has been redefined as a secondary endpoint instead of a component of the primary composite-event endpoint per Regulatory Authority request.
7. Histological confirmation (biopsy) has been added as an acceptable method of confirming a diagnosis of HCC.
8. **Broadening the Spectrum of Disease**: Lowering the minimum allowable baseline ALP from >5x ULN to >3x ULN and raising the maximum allowable baseline total bilirubin to ≤5x ULN will increase the number of subjects enrolled with early and advanced disease facilitating the collection of safety and efficacy data in a population that covers the spectrum of PBC disease and overlaps with the subject population in the Phase 3 protocol 747-301. However, to ensure enrollment of an adequate number of subjects with abnormal total bilirubin, a minimum of 30% of the subjects enrolled in the study will have elevated bilirubin (>ULN) at Screening.
9. The titration regimen has been updated to reflect assessment of both tolerability and biochemical response prior to up-titration per the USPI and SmPC.
10. The increase in enrollment from 350 to 428 subjects is due in part to the increased number of events from two additional interim analyses, and in part due to the change in the estimated placebo baseline hazard rate, which resulted from changing the lower limit of ALP from >5x ULN to >3x ULN in the enrollment criteria #2.
11. **Progression to Cirrhosis** has been added as a secondary endpoint: Due to the chronic nature of PBC, outcomes require a very long time to accrue to evaluate the impact of potential therapies. Despite the proven prognostic utility of ALP and bilirubin, there is a remaining need to evaluate noninvasive assessments of disease progression that can be linked to histological progression of the disease. Therefore, it is important to evaluate potential noninvasive markers of fibrosis/cirrhosis and their relationship to clinical outcomes as part of Study 747-302.
12. **A Per Protocol (PP) population** has been added to the statistical analysis section. Sensitivity analysis for primary efficacy endpoints and key secondary efficacy endpoints will be performed using PP population.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Title Page Synopsis, Title of Study	A Phase ~~3b~~, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary ~~Cirrhosis~~	A Phase **4**, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary **Cholangitis**	Rationale 1 and 2
Study Personnel Contact Information	**Or if Not Available:** Contact: PPD ~~MD, PhD, Executive Director, Clinical Research~~, Intercept Pharmaceuticals, Inc. Telephone: PPD Mobile: PPD (Pacific time zone) Email: PPD PPD **~~Clinical Operations and Project Management~~** ~~Contact:~~ PPD PPD ~~Clinical Operations,~~ ~~Intercept Pharmaceuticals, Inc.~~ ~~Telephone:~~ PPD ~~(Pacific time zone)~~ ~~Mobile:~~ PPD ~~Fax:~~ PPD ~~Email:~~ PPD	**O**	The contact information of clinical operations and project managements personnel is no longer required per Sponsor's procedures.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Studied Period (Years)	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3 and 4
Synopsis, Phase of Development	Phase ~~3b~~	Phase **4**	Rationale 1
Synopsis, Objectives, Primary, Statistical Methods – Efficacy Analyses Section 6.1 Primary Objective Section 11.1.1 Primary Assessments Section 13.1.3 Primary Efficacy Analysis	• Encephalopathy (as defined by a West Haven score of ≥2) • ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~	• **Hepatic** encephalopathy (as defined by a West Haven score of ≥2)	Rationale 5 Rationale 6
Synopsis, Objectives, Secondary Section 6.2 Secondary Objectives	To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above ~~and also~~ to include liver related death.	To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above. **To assess the effect of OCA compared to placebo on time to occurrence of** liver-related death.	Rephrasing the objective

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Insertion	**To assess the effect of OCA compared to placebo on progression to cirrhosis.**	
		To assess the effect of OCA compared to placebo on time to occurrence of hepatocellular carcinoma (HCC).	Rationale 11
		To **characterize** the pharmacokinetics of OCA and its conjugates in a subset of subjects	Rationale 6
	To ~~assess~~ the pharmacokinetics of OCA and its conjugates in a subset of subjects		
Synopsis, Methodology:		**A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.**	Rationale 8
Schematic Diagram			Rationale 8
Section 7.1.1 Study Design Diagram, Figure 1	Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability.	Initial dose titration of investigational product should occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response (up-titration should be considered when ALP and/or total bilirubin are >ULN)**.	Rationale 9
	• Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product.	• Subjects should titrate to a maximum dose of 10-mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability **and biochemical response** of the product.	
	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once	• Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5-mg OCA or matching placebo once daily, based on tolerability **and biochemical**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	daily, based on tolerability. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability. Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	**response**. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10-mg OCA or matching placebo twice weekly, based on tolerability **and biochemical response.** Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (Table) [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study.	
Synopsis, Number of Subjects (Planned) Section 7.2 Number of Subjects	***Insertion*** ***Change in Synopsis section*** Approximately ~~350~~ subjects ***Change in Section 7.2 section*** It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	**In the event additional subjects are needed for the enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the sub study may be added to the target subject enrollment number currently planned**. Approximately **428** subjects **are planned to be enrolled in the study.** It is expected that approximately **428** subjects will be randomized in the study to achieve **127** adjudicated primary endpoint events.	Rationale 10 and Addendum 2

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	2. A mean total bilirubin >ULN and ~~≤3~~x ULN and/or a mean ALP >~~5~~x ULN	2. A mean total bilirubin >ULN and ≤**5**x ULN and/or a mean ALP >**3**x ULN	Rationale 8
Synopsis, Inclusion Criteria Section 8.2 Subject Inclusion Criteria	5. Contraception: Female subjects 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: • ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~; or~~ • Intrauterine device (IUD)~~; 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 subject	5. Contraception: Female subjects **of childbearing potential** must use ≥1 effective method of contraception during the study and **until** 30 days **following** the **last dose of investigational product**. Effective methods of contraception are considered to be those listed below: • **Barrier** method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide • Intrauterine device (IUD) • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) • Abstinence, if in line with the preferred and usual lifestyle of the subject	Standardizing language across protocols; removing double-barrier terminology.
Synopsis, Exclusion Criteria Section 8.3 Subject Exclusion Criteria	2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:	2. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including: **•History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as**	This criterion (sub-bullet) is already included in Version 3 of the protocol. In the

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td>3. Mean total bilirubin >~~3~~x ULN</td><td>long as they do not meet any of the other exclusion criteria
3. Mean total bilirubin >5x ULN</td><td>Version 4, it is added to the synopsis for consistency.

Rationale 8</td></tr>
<tr><td><u>Synopsis,</u> Duration of Treatment</td><td>It is ~~estimated~~ that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue ~~121~~ total primary endpoint events.</td><td>It is expected that subjects will be followed up for a minimum of 6 years. The study is event driven and total duration of treatment will be determined by the time to accrue 127 total primary endpoint events.</td><td>Rationale 3</td></tr>
<tr><td><u>Synopsis</u>, Criteria for Evaluation</td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Encephalopathy (as defined by a West Haven score of ≥2)
• ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~</td></tr><tr><th>Secondary Objectives</th><th></th></tr></table></td><td><table><tr><th>Primary Objectives</th><th>Assessments</th></tr><tr><td>Clinical outcomes</td><td>– Hepatic encephalopathy (as defined by a West Haven score of ≥2)</td></tr><tr><th>Secondary Objectives</th><th></th></tr><tr><td>Progression to cirrhosis</td><td>Clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (i.e., Fibroscan® TE) confirmed by biopsy unless not medically indicated</td></tr><tr><td>Hepatocellular carcinoma</td><td>Confirmed by 2 complimentary imaging modalities unless confirmed by biopsy</td></tr></table></td><td>Rationale 5

Rationale 11

Rationale 6</td></tr>
<tr><td><u>Synopsis</u>, Statistical Methods
Analysis Populations</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: ~~Randomized~~, Intent-to-Treat (ITT), Safety, PK, Overall Historical Control, UKPBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.</td><td>The following subject populations will be evaluated and used for presentation and analysis of the data: Intent-to-Treat (ITT), Per Protocol (PP) Safety, PK, Overall Historical Control, UK-PBC Historical Control, and the Global PBS Historical Control. Descriptions of subject populations are provided in Section 13.1.1.</td><td>Randomized population includes patients on OCA who withdrew prior to receiving drug and this is already collected with the safety population.

Rationale 12 (for PP Population)</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Synopsis, Statistical Methods, Primary Efficacy Endpoint Section 11.1.1 Primary Assessments	The primary efficacy endpoint will be the time to first occurrence of one of the following ~~post randomization~~: • Encephalopathy (as defined by a West Haven score of ≥2) • ~~Hepatocellular carcinoma confirmed by 2 complimentary imaging modalities~~ ***Change in Synopsis section*** ~~Every event for enrolled subjects~~ will be adjudicated by an independent committee.	The primary efficacy endpoint will be the time to first occurrence of one of the following: • **Hepatic** encephalopathy (as defined by a West Haven score of ≥2) **All events** will be adjudicated by an independent committee.	Rationale 5
Synopsis, Statistical Methods, Primary Efficacy Analysis Section 13.1.3 Primary Efficacy Analysis	The primary efficacy analysis will compare ~~randomized~~ OCA to ~~randomized~~ placebo with respect to the primary efficacy endpoint using the ITT population. ***Insertion***	The primary efficacy analysis will compare OCA to placebo with respect to the primary efficacy endpoint using the ITT population. **The same analyses for primary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	Rationale 12
Synopsis, Statistical Methods, Key Secondary Efficacy Analyses Section 13.1.4 Secondary Efficacy Analysis	The key secondary efficacy analyses will compare ~~randomized~~ OCA to ~~randomized~~ placebo in ITT population with respect to the key secondary efficacy endpoints. ***Insertion***	The key secondary efficacy analyses will compare OCA to placebo in **the** ITT population with respect to the key secondary efficacy endpoints. **The same analyses for key secondary efficacy endpoints will be performed for PP population as a sensitivity analysis.**	Rationale 12
Synopsis, Statistical Methods, Additional Efficacy Analyses	~~Other~~ Efficacy Analyses The following secondary efficacy analyses will compare OCA to placebo ~~on time to the following events~~:	**Additional** Efficacy Analyses The following **time-to-event** secondary efficacy analyses will compare OCA to placebo **using the ITT population**: • **Progression to cirrhosis** • **Time to occurrence of HCC**	Rationale 6 and Rationale 11

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.5 Additional Secondary Efficacy Analyses	***Insertion***	**Progression to cirrhosis will be assessed in the subset of subjects considered noncirrhotic at Baseline using available medical history, clinical, and laboratory assessments as well as Baseline transient elastography (TE), where available. Specifically, subjects with no clinical, laboratory, or radiological evidence of cirrhosis at baseline and/or a TE liver stiffness of <16.9 kPa (Corpechot 2012) will be considered noncirrhotic. Progression to cirrhosis will be assessed by the development of clinical, laboratory, or radiological evidence of cirrhosis and/or when liver stiffness increases to ≥16.9 kPa during the study in which case histological progression to cirrhosis should be confirmed by biopsy unless not medically indicated. Using this definition for progression to cirrhosis, the percentage of noncirrhotic subjects progressing to cirrhosis during the treatment period will be summarized by treatment group and compared using a Cochran–Mantel–Haenszel test stratified by the randomization stratification factor.** **For those subjects enrolled in the biopsy substudy (defined in Addendum 2) progression to cirrhosis identified by the above criteria and improvement in fibrosis/cirrhosis will be confirmed by paired biopsy. Analyses for the histological assessment conducted as part of the biopsy substudy are defined in Addendum 2.**	Rationale 11
Synopsis, Statistical	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results	Safety data, including AEs, vitals, electrocardiogram, and clinical laboratory results	Clarification of summary analyses.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Methods, Safety Analyses	will ~~compare OCA and placebo using~~ the Safety Population.	will **be summarized by treatment group for** the Safety Population.	
Synopsis, Statistical Methods, Sample Size Justification Section 13.1.2. Determination of Sample Size	The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.~~5~~ at 8 years with a hazard ratio of 0.60, and total study duration of ~~8~~ years, allowing for ~~2~~ years accrual and 6 years of follow up ***Insertion*** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of ~~121~~ events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to ~~clinical outcomes~~. In addition, based on the remaining assumptions stated above, it is estimated that approximately ~~350~~ subjects will be enrolled to attain ~~121~~ events.	**The target population is subjects who are at higher risk of liver-related clinical complications. Eligible subjects will have a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP >3x ULN.** The following assumptions were used in sample size calculations: • Exponential survival curves, placebo survival estimate of 0.**6** at 8 years with a hazard ratio of 0.60, and total study duration of **10** years **(from first subject enrolled)**, allowing for **4** years **of subject** accrual and 6 years of follow up. • **Two interim analyses and one final analysis are planned. The first interim analysis will be performed when 50% of the target events are accrued and the second interim will be performed when 75% of the target events are accrued.** • **A dropout rate of 10% is assumed** Based on the randomization ratio, significance level, and assumed hazard ratio, a total of **127** events (both groups combined) will provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to **liver-related outcomes, including all-cause mortality**. In addition, based on the remaining assumptions stated above, it is estimated that approximately **428** subjects will be enrolled to attain **127** events.	Rationale 8 Rationale 4 Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 5.1 Overview of PBC and OCA	5.1. Overview of Primary Biliary ~~Cirrhosis~~ and Obeticholic Acid Primary biliary cholangitis, (PBC, also known as primary biliary cirrhosis) 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. ursodeoxycholic acid (UDCA), a physiological constituent of human bile, ~~is currently the only treatment approved for PBC~~ (Lindor 2009). While UDCA therapy ~~has~~ a marked effect on the treatment of PBC, up to 50% of patients ~~show~~ a suboptimal response or no response to UDCA. Such patients ~~are~~ at significantly increased risk of a poor clinical outcome due to PBC disease progression. ~~There is a clear unmet medical need for better therapies for patients with PBC that have an inadequate response to UDCA, or those who cannot tolerate UDCA (typically due to gastrointestinal adverse events [AEs]).~~ Obeticholic acid (OCA) ~~is being developed for the treatment of PBC and to provide patients that have an inadequate response to or poor tolerance of UDCA a novel treatment option that is safe and effective.~~ ~~OCA is a modified bile acid and~~ farnesoid X receptor (FXR) agonist ~~that is~~ derived from the primary human bile acid chenodeoxycholic acid (CDCA~~). OCA is currently being developed in the United States (~~US) and Europe for the treatment of PBC and other chronic liver diseases. OCA has~~	5.1. Overview of Primary Biliary **Cholangitis** and Obeticholic Acid 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. **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), **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 (Pellicciari 2002). 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**	Updating language to include accelerated and conditional approvals of OCA in the US and EU.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. The United States~~ Food and Drug Administration (FDA) ~~has~~ granted accelerated approval for Ocaliva ~~for the treatment of PBC.~~ Ocaliva ~~is not yet approved outside the United States for use in any~~ indication.	**UDCA. In December 2016, the European Commission granted conditional approval for** Ocaliva **for the same** indication.	
Section 5.4 Overview of PBC and OCA	As of 31 Jan ~~2016~~, approximately ~~1726~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~458~~ subjects had PBC, ~~330~~ subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease ~~(NAFLD)~~, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~20~~ subjects had primary sclerosing cholangitis (~~PSC~~).	As of 31 Jan **2017**, approximately **2186** subjects[1] have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, **525** subjects had PBC, **686** subjects had NASH, 41 subjects had diabetes mellitus/non-alcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **52** subjects had primary sclerosing cholangitis, **and 5 subjects had biliary atresia.** **----------** **[1]Includes estimated numbers from ongoing blinded studies.**	Language updated to include data from current IB.
Section 5.5.2.1 Rationale for OCA Dose	The Phase 3 PBC study subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; ***Insertion***	The Phase 3 PBC study **(Study 747-301)** subsequently evaluated the safety and efficacy of OCA at lower doses of 5 mg (titrated to 10 mg after 6 months based on efficacy and tolerability in the double-blind phase and after 3 months in the open-label phase) and 10 mg; **Study 747-301 demonstrated that titration of OCA from a starting dose of 5 mg to 10 mg improved tolerance to pruritus relative to 10 mg (56% versus 69% of subjects who experienced pruritus) and minimized dropouts due to pruritus.** Based on these data, the **approved dosing regimen for** OCA for the treatment of patients with PBC are 5 mg and 10 mg.	Provides rationale for the dosing in alignment with commercial labeling.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Based on these data, ~~the indicated commercial doses of~~ OCA for the treatment of patients with PBC are 5 mg and 10 mg. ~~As such,~~ Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose increasing to 10 mg OCA, if tolerated.	Study 747-302 will evaluate the effect of OCA on clinical outcomes using the 5 mg OCA dose **for at least 3 months**, increasing to 10 mg OCA, if tolerated.	
Section 5.6 Summary of Known Potential Risks with OCA	These findings were seen more frequently with doses ~~above~~ 10 mg OCA. ***Insertion***	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).** **Refer to the Investigator's Brochure (IB) for additional information regarding the known potential risks with the investigational product.**	Language has been updated to reflect Sponsor standards.
Section 7.1 Overall Study Design	This is a Phase ~~3b~~, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤~~3~~× ULN or ALP >~~5~~× ULN. Approximately ~~350~~ subjects meeting all enrollment criteria will be recruited into the study over an approximate ~~2~~-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). ~~Investigational product will be taken orally, once daily~~….based on tolerability (see Section 7.3).	This is a Phase **4**, double-blind, randomized, placebo-controlled, multicenter study. Eligible subjects will have a diagnosis of PBC with bilirubin levels of >ULN and ≤**5x** ULN and/or ALP >**3**x ULN. Approximately **428** subjects meeting all enrollment criteria will be recruited into the study over an approximate **4**-year period, randomly allocated to treatment with either OCA or matching placebo in a 1:1 ratio (Figure 1). . . **A minimum of 30% of subjects will have elevated bilirubin (>ULN) at Screening.** **Subjects will be dosed according to their cirrhosis status and Child-Pugh Score**…based on tolerability **and biochemical response** (see Section 7.3)	Rationale 1 and Rationale 8 Rationale 10 Rationale 8 Clarification Rationale 9

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	The study will continue until approximately ~~121~~ adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	The study will continue until approximately **127** adjudicated primary endpoint events have been accrued in unique subjects, or until the Sponsor (eg, based on advisement by the Data Monitoring Committee; DMC) terminates the study.	Rationale 3
Section 7.1.2 Schedule of Study Procedures, Table 1	***Insertions***	Physical exams have been added at: • **Month 1** • **1-Month Post Titration** • **Month 6** Fibroscan® TE has been added at **Month 6** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.
	[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility.	[a] All subjects will have the chemistry panel retested to ensure subjects have at least two ALP and bilirubin assessments at least 2 weeks apart to calculate the mean result for both analytes. The mean of all screening ALP and bilirubin assessments will be used to determine eligibility. **Refer to Section 9.7.6 for guidance on when an additional ALP or bilirubin sample may be needed to confirm eligibility.**	
	[j] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available.~~	[j] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available.	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis
	Insertion (subsequent footnotes are renumbered accordingly)	[k] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure.**	DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[k] Endoscopy will be conducted at ~~selected~~ study sites where the device is available. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (eg, post-Day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met~~. [o] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability. … [u] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12.	[m] Endoscopy will be conducted at **all** study sites where the device is available**.** [m] 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**. [p] … The initial dose titration of investigational product may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response**. … [v] A genetics study will be conducted in a subset of subjects who provide consent for analyses of these samples. Genetics samples will be collected at Day 0 and every other year beginning at Month 12. **If a Baseline (eg, Day 0) genetic sample is not obtained, subsequent genetic samples are not required to be collected during the course of the study.**	annual assessments at Day 0 and Month 12). Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis. Rationale 9 Clarification
Section 7.1.2 Schedule of Study Procedures, Table 2	***Insertions***	Physical exams have been added at **1-Month Post Titration** Fibroscan® TE has been added at **Month 6 continued follow up** **DEXA** has been moved to its own line Hepatic Ultrasound has been added at **Month 6 continued follow up**	Physical Exams have been added one month after each dose adjustment for added safety monitoring.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	[i] Transient elastography (TE) will be conducted at ~~selected~~ study sites where the Fibroscan® TE device is available. ~~Similarly, DEXA will be conducted at selected study sites where the DEXA device is available. Not required if done within 6 months of visit.~~ ***Insertion*** (subsequent footnotes are renumbered accordingly) [j] Endoscopy will be conducted at ~~selected~~ study sites where the device is available to assess for the presence of oesophageal varix/varices. [k] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. post-day 0) ultrasounds: ~~If a lesion is found~~, a second confirmatory image (eg, MRI) should be obtained to confirm ~~if a study endpoint has been met.~~ [e] … The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability.	[i] Transient elastography (TE) will be conducted at **6-month intervals at all** study sites where the Fibroscan® TE device is available. [j] **DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available.** [k] Endoscopy will be conducted at **all** study sites where the device is available to assess for the presence of oesophageal varix/varices. [l] Ultrasound will be conducted to enhance HCC surveillance. For all on study (e.g. 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**. [o] … The initial dose titration of investigational products may occur at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability **and biochemical response.**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis. DEXA has been separated from Fibroscan® TE to allow additional monitoring of the latter (the schedule for DEXA exams has not changed from annual assessments). Hepatic ultrasound monitoring has been increased to every 6 months to conform to AALSD and EASL practice guidelines for PBC patients with cirrhosis. Rationale 9
Section 7.1.3 Study Duration	The study is event driven and total duration will be determined by the time required to accrue approximately ~~121~~ primary endpoint events, estimated to be approximately ~~8~~ years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	The study is event driven and total duration will be determined by the time required to accrue approximately **127** primary endpoint events, estimated to be approximately **10** years. Subjects are expected to have a minimum follow-up time of approximately 6 years.	Rationale 3

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 7.2 Number of Subjects	It is expected that approximately ~~350~~ subjects will be randomized in the study to achieve ~~121~~ adjudicated primary endpoint events.	It is expected that approximately **428** subjects will be randomized in the study to achieve **127** adjudicated primary endpoint events. **In the event additional subjects are needed to complete enrollment in the biopsy substudy (N = 45 subjects, as defined in Addendum 2), subjects who agree to participate in the substudy may be added to the target subject enrollment number currently planned**.	Rationale 10 Language added to allow for continued enrollment into the biopsy substudy; additional subjects are not anticipated to prolong the duration of the study.
Section 7.3 Planned Dosing Regimen, and Table 3	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product. ***Footnotes of Table 3 were re-ordered*** ~~b~~ Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Subjects should titrate to a maximum dose of 10 mg OCA once daily (or matching placebo) at the Month 3 visit or at any study visit following the Month 3 visit based on tolerability of the product **and assessment of biochemical response. Up-titration should be considered if ALP and/or total bilirubin are >ULN**. [c] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, **biochemical response**, and/or changes in cirrhosis status or Child-Pugh score at any time during the study	Rationale 9
Section 7.4 Dose Titration Criteria	***Insertion***	**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) as well as biochemical response (as assessed by reductions in ALP and/or total bilirubin). In general, down-titration will be done in response to tolerability concerns and can occur at any time while on-study. Up-titration will be done per protocol when subjects have no tolerability concerns and have not achieved an adequate reduction in ALP and/or total bilirubin to within normal limits, or as**	Added language to clarify titrations (up or down).

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	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.	**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 for each dosing regimen as defined in Section 7.3.** 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, **biochemical response**, and clinical judgment. **Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately and should not necessarily result in a change to the dosing regimen (Appendix A).**	
Section 7.4.1 Pre-Titration Tolerability Assessment Requirements	• There must be no clinically significant increase (as determined by the ~~i~~nvestigator) in the subject's liver function tests. ~~Subjects whose total bilirubin is >2× baseline (and >ULN) cannot be up-titrated, and additional unscheduled safety visit procedures, outlined in Section 9.7.19 should be implemented, as required.~~	• There must be no clinically significant increase (as determined by the **I**nvestigator) in the subject's liver function tests.	Clarification
Section 7.4.2 Safety Criteria for Adjustment or Stopping Doses	***The text in this section is moved to Section 8.4.***		To avoid redundancy
Section 7.5 Criteria for Study Termination	The window of time for scheduling the visit will be based on a final projection of when the requisite ~~121~~ adjudicated events will have been accrued.	The window of time for scheduling the visit will be based on a final projection of when the requisite **127** adjudicated events will have been accrued.	Rationale 3
Section 8.4	**[*Moved from Section 7.4.2 of Version 3*]**		Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or 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 that 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 when the needed number of adjudicated events has accrued. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be **adjusted back** to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved. Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an **outcome** event, he or she should continue the regular visit schedule and continue taking investigational product as long as the **subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the** Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.	
Section 8.4.1.1 Reasons for Additional Monitoring Related to Liver Chemistries	***Modification of 8.4.2.1 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~~	**Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored.**	Clarified guidelines for subjects who develop elevations in liver chemistries. Language related to interruption of investigational product is now located in Section 8.4.1.2.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~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.~~		
Section 8.4.1.2 Reasons for Investigational Product Interruption Related to Elevated Liver Chemistries	***Insertion***	**Development of any of the following clinical laboratory values, without explanation, during the study mandates investigational product interruption:** • **AST and/or ALT >3x baseline (and >ULN)** • **Total bilirubin >2x 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 AE information should also be collected and the subject 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 >3x baseline (and >ULN) or total**	Clarified guidelines for subjects who develop elevations in liver chemistries.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		bilirubin >2x baseline (and >ULN), subjects 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 investigative product and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject 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.**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		If at any time a subject 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. **Subjects who develop evidence of severe drug-induced liver injury, which 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 subjects 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**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		appropriate for the subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time. **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 13.4).**	
Section 8.4.1.3 Pregnancy	***Modification*** of 8.4.1 Reasons for Mandatory Discontinuation of Investigational Product If a female subject becomes pregnant, she must ~~discontinue taking~~ investigational product, but should continue with the study visit schedule. ~~The subject must be followed as considered appropriate by the Investigator and the medical monitor through pregnancy outcome. For reporting purposes~~ pregnancy is not considered an AE. The subject may ~~reinstate~~ investigational product ~~after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator. ~~Subjects whose pregnancy is terminated early (planned or unplanned) may be permitted to resume participation in the study if termination of the pregnancy is confirmed by a serum beta human chorionic gonadotropin (β-hCG) test performed at the central laboratory.~~	**8.4.1.3 Pregnancy** If a female subject becomes pregnant, she must **interrupt treatment with** investigational product **immediately,** but should continue with the study visit schedule. **As described in Section 12.1.11** pregnancy is not considered an AE **for reporting purposes.** The subject may **re-start** 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 12.1.11.**	Clarification regarding prolonged interruption in investigational product such as in the event of pregnancy.
Section 8.4.2.1 Liver Transplantation	***Text Moved from Section 8.4.2 Other Reasons for Discontinuation of Study or Investigational Product***	**8.4.2.1 Liver Transplantation** Subjects who undergo a liver transplant during the course of the study must discontinue	The relocation of this statement from within Section 8.4.2 to 8.4.2.1 clarifies procedure to discontinue subjects who

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.	investigational product and discontinue the study visit schedule. However, these subjects 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.	undergo a liver transplant, from investigational product but not study visits.
Section 8.4.3 Other Reasons for Discontinuation of Study or Investigational Product	8.4.2 Other Reasons for Discontinuation of Study or Investigational Product ~~Subjects that discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. If a subject reaches an event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who choose to discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Early termination procedures should only be conducted if the subject withdraws consent (See Section 9.7.18 Early Discontinuation and/or Early Termination Procedures).~~ The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination ~~and the study will only terminate at the time when the needed number of adjudicated events has accrued~~ (or at the discretion of the Sponsor):	**8.4.3** Other Reasons for Discontinuation of **Study or** Investigational Product The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor):	Clarification of process

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	– Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess for ~~potential adjudicated hepatic and/or~~ cardiovascular events. ~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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.~~	– Consent may be modified to discontinue study visits or semi-annual telephone contact but allow continued access to medical records to assess **suspected major adverse** cardiovascular events **(MACE) and liver-related clinical outcomes.** – **Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.18).** **The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment.**	
Section 9.7.1 Visit Windows	Screening |	Screening | **See Section 9.7.6 for scenario specific visit windows that may be applicable at Screening.**	
Section 9.7.3.1 Determination for Dosing Regimen	***Insertion*** Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of ~~the study~~ is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	**9.7.3.1 Determination for Dosing Regimen** Acceptable methods of confirming (via medical history) or assessing cirrhosis for purposes of **determining dosing** is defined as a subject who has documented evidence or presence of one or more of the following cirrhosis indicators:	Header added to differentiate the assessment of cirrhosis for determining dosing regimen versus progression to cirrhosis.
Section 9.7.3.2 Progression to Cirrhosis	***Insertion***	**9.7.3.2 Progression to Cirrhosis** **When a subject identified as noncirrhotic at Baseline per the criteria listed in Section 9.7.3.1 exhibits any signs or symptoms associated with progression to cirrhosis, as defined by the same criteria, the subject should also be assessed by Fibroscan® TE where available and progression to cirrhosis**	Details the assessment of progression to cirrhosis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		confirmed by biopsy (centrally read) unless not medically indicated. Laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF, and aspartate aminotransferase to platelet ratio index [APRI]) will also be collected when a subject develops evidence of progression to cirrhosis. **Full instructions concerning the sample collection methods, processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory.** **Sites participating in the paired biopsy substudy must confirm progression to cirrhosis by biopsy as per the information outlined in protocol Addendum 2.** **All suspected cases of progression to cirrhosis should be submitted for adjudication regardless of the availability of transient elastography or biopsy results.**	
Section 9.7.6 Screening Procedures	~~Two Screening visits will occur from 1 to 8 weeks prior to Day 0 (as outlined below) allowing for the collection of repeated~~ serum chemistry samples (at least 2 weeks apart) ~~to confirm~~ pretreatment ALP and total bilirubin values: ***Insertion***	**Collection of 2 s**erum chemistry samples (**collected** at least 2 weeks apart**) during Screening is required for confirmation of the** pretreatment **serum chemistry values, including the** ALP and total bilirubin **used to determine eligibility**: • **When the 2 bilirubin or ALP assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Allows repeat assessments when baseline laboratory values are discrepant between Screening Visit 1 and Screening Visit 2.

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	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤~~3~~× ULN and/or an ALP >~~5~~× ULN). • …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 (~~selected~~ study sites ~~only~~), ***Insertion***	• The mean of all available (at least 2; including both scheduled and unscheduled) bilirubin and ALP assessments will be used to determine eligibility (total bilirubin >ULN and ≤**5x** ULN and/or an ALP >**3x** ULN). • …the dual-emission X-ray absorptiometry (DEXA) bone density scan to be done at Day 0 **(at all** study sites **where the device is available**), **In the event that the 2 screening bilirubin or ALP assessments differ by ≥30%, and a third confirmatory sample is required to be collected, the Screening Visit window may be extended up to 3 additional weeks.**	
Section 9.7.7 Day 0 Procedures	• Perform ~~transient elastography (~~TE~~;~~ at ~~selected~~ study sites~~, where available) using the~~ Fibroscan® TE device. If TE has been done within ~~6~~ months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at ~~selected~~ study sites~~,~~ where device is available); • Perform an esophagogastroduodenoscopy (endoscopy; at ~~selected~~ study sites, where device is available) to assess the presence or absence of oesophageal varix/varices.	• Perform TE at **all** study sites **with access to** Fibroscan® TE device. If TE has been done within **3** months of Day 0 and a report/adequate data are available, a pretreatment TE at Day 0 is not required. • Conduct a DEXA bone density scan (at **all** study sites where **the device is** available); • Perform an esophagogastroduodenoscopy (endoscopy; at study sites, where **device is** available) to assess the presence or absence of oesophageal varix/varices.	Clarifies use of TE and modifies the time during which an historic TE report remains valid. Clarifies the use of DEXA and endoscopy.
Section 9.7.8 Month 1 Procedures Section 9.7.10	9.7.10 Post-Titration visit Procedures ***Insertion*** • In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit	9.7.10 **1-Month** Post-Titration visit Procedures • Perform a physical examination. • In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure	Physical Exams have been added one month after each dose adjustment for added safety monitoring. Options for safety monitoring assessments are provided when returning to the site

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
1-Month Post-Titration visit Procedures	procedures are available to help ensure compliance with the Month 1 visit requirements: ***Insertion (9.7.8)*** ***Insertion (9.7.10)***	compliance with the Month 1 visit **laboratory** requirements: - **A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed**. - **A physical examination should be performed at the next scheduled visit if an onsite post-titration visit was not performed**.	presents significant burden on the subject.
Section 9.7.11 Month 6 Procedures Section 9.7.16 Month 6 Continued Follow-Up Procedures	***Insertion*** ***Insertion in 9.7.11 (not 9.7.16)***	• **Perform TE at all study sites with access to Fibroscan® TE device.** • **Perform an ultrasound for HCC surveillance (if equipment is unavailable, sites should make every attempt to use available community referral sites).** • **Perform a physical examination**	Fibroscan® TE monitoring has been increased to every 6 months to facilitate monitoring for progression to cirrhosis. Hepatic ultrasound has been increased to every 6 months to conform to AASLD and EASL guidelines for PBC patients with cirrhosis.
Section 9.7.12 Month 9 Procedures Section 9.7.14 Month 12 Procedures Section 9.7.16 Month 16 Continued Follow-Up Procedures	*...DEXA procedure to be done at* ~~selected~~ study sites ~~only~~,	*...DEXA procedure to be done at* **all** study sites **where the device is available**	Clarification

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 9.7.14 Month 12 Procedures Section 9.7.17 Month 12 Follow-up Procedures Section 9.7.18 EOS/EOT	• Perform TE ~~(~~at ~~selected~~ study sites~~, where available) using the~~ Fibroscan® TE device. ***Additional edit in Section 9.7.18*** - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF ~~and remind the subject that fasting is required prior to all study visits~~.	• Perform TE at **all** study sites **with access to the** Fibroscan® TE device. - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF.	Clarification
Section 10.3 Investigational Product Storage	~~The investigational product should be stored in the containers in which they are received from the Sponsor's supplier, at 15°C to 25°C.~~	**All OCA tablet strengths provided to clinical trial sites in support of clinical study 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.**	Updating temperature excursions language per Sponsor stability studies.
Section 11.1.2 Secondary Assessments	***Insertion***	• **Individual components of the primary endpoint.** • **Progression to cirrhosis as assessed by the presence of clinical, laboratory, or radiological evidence of cirrhosis and/or liver stiffness (Fibroscan® TE), confirmed by biopsy unless not medically indicated.** • **Histological assessment of disease progression or improvement using paired biopsies in a subset of subjects (defined in Addendum 2).** – **HCC confirmed by 2 complimentary imaging modalities, unless confirmed by biopsy.**	Rationale 11 Reflects addition of a biopsy substudy available to interested sites in Addendum 2.

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td>• Biomarkers, including markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) <s>and</s> ELF, Fibroscan (and others as determined during the course of the study).

• Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.</td><td>• Biomarkers, including other markers of hepatic fibrosis and/or inflammation, to be tested will include: IgM, c-reactive protein (CRP), tumor necrosis factor-α (TNF-α), FGF-19, cytokeratin-18 (CK-18) ELF, and Fibroscan (and others as determined during the course of the study).
• Clinical outcomes, including individual component of the primary endpoint (where available), liver transplant, and death will be compared to historical controls.
• PK of OCA and its conjugates.
• Endoscopy will be conducted at all study sites where the device is available to assess for the presence of oesophageal varix/varices at baseline.</td><td></td></tr>
<tr><td>Section 12.1.3
Relationship of AEs to Liver Biopsy</td><td>Insertion (new section)</td><td>The Investigator will document her/his opinion of relationship of an AE to liver biopsy using the criteria outlined in Table 9.
Table 9: Relationship of Adverse Events to Liver Biopsy
<table>
<tr><th>Relationship</th><th>Description</th></tr>
<tr><td>Related</td><td>A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.</td></tr>
<tr><td>Not Related</td><td>Any event that does not meet the above criteria.</td></tr>
</table></td><td>Added with the addition of liver biopsies for the confirmation of progression to cirrhosis.</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 12.1.5.2 Reporting of Serious Adverse Events	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 ~~•Telephone: +1 858 964 1571~~ ~~Investigational new drug (IND) Safety Reports~~ ***Insertion***	If an SAE is reported by **email** or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible **Redacted medical record source documentation will be requested for all SAEs and emergency room visits.**	Updated to align with modified standard safety procedures. Added sentence regarding redacted medical records to align with Sponsor safety standards.
Section 12.1.6 Suspected Liver-Related Clinical Outcome Events	~~For~~ liver-related clinical outcome events ~~could~~ also meet the criteria of a SUSAR, ~~which would necessitate unblinding for expedited reporting, please refer to Section 11.1.2.4.~~ The Sponsor will consider the following list of clinical outcome events (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), hepatic encephalopathy (preferred	**Given that the** liver-related clinical outcome events **may** also meet the criteria of a SUSAR, **but are considered in aggregate as part of the primary endpoint and the DMC reviews of all safety and efficacy data at least quarterly, the Sponsor will not expeditiously report suspected liver-related 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 "study event" on the AE CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 13.4**. The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a nonexpeditious 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 **or oesophageal varices**	Updated to align with modified standard safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	term: hepatic encephalopathy), ~~and~~ spontaneous bacterial peritonitis (preferred term: peritonitis bacterial).	**haemorrhage**), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), **ascites (preferred term: ascites), and histological or clinical progression to cirrhosis (preferred term: hepatic cirrhosis).**	
Section 12.1.8 Notification of Post-Treatment SAEs for Subjects Who Continue in the Study	***Insertion (new section)***	**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 12.1.5.2.** **SAEs that occur in subjects 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 12.1.5.2.**	Updated to align with modified safety procedures and Sponsor standard language.
Section 12.1.9 Notification of Poststudy SAEs	All SAEs that occur within 30 days following the ~~cessation of investigational product~~, 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 12.1.~~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 SAE must be reported to~~ the Sponsor immediately (ie, within 24 hours). ~~SAEs that occur more than 30 days after a subject has discontinued investigative product, and are not considered related to investigational product, must still be reported in the EDC system; however, these events are not required to be reported within 24 hours. At a minimum, the SAE term, event start and end date, severity, relationship to~~	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 12.1.**5**.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 12.1.5.2.	Updated to align with modified safety procedures and Sponsor standard language.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~investigational product, action taken with investigative product, treatment, outcome, and potential endpoint status need to be recorded in EDC for the SAE. Additional information (e.g. event summary, SAE details) may also be required to be entered, when requested by the sponsor.~~		
Section 12.1.10 Follow-up of AEs and SAEs	***Insertion***	**All subjects 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 CRF. 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.**	Updated to align with modified standard safety procedures and Sponsor standard language.
Section 12.1.11 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 8.4.1.3and the Sponsor must be notified within 24 hours of the Investigator's ~~learning~~ of the pregnancy by completing the Pregnancy ~~Notification~~ Form ~~and faxing or emailing~~ to ~~the Sponsor at +1 800 497 8521 or~~ sae@interceptpharma.com. ~~Safety will be monitored and assessed by AEs/SAEs, medical history, physical examination, vital signs measurements, ECG results, and clinical laboratory assessments. The Sponsor may also follow the health of an infant born subsequent to use~~ of investigational product. ~~The subject may reinstate investigational product after delivery and cessation of~~ breastfeeding (if applicable) at the discretion of the Investigator.	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** sae@interceptpharma.com **or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor**. **The subject may restart** investigational product **when she is no longer pregnant or**	Updated to align with modified standard safety procedures and Sponsor standard language.

<table>
<tr><th>Section</th><th>Original Text (Amendment 3, 07 September 2016)</th><th>Revised Text (Version 4, 10 May 2017)</th><th>Justification for Change</th></tr>
<tr><td></td><td>~~Subjects whose~~ pregnancy is terminated early (planned or unplanned) ~~may be permitted to resume participation in the study if~~ termination of the pregnancy ~~is~~ confirmed by a serum β-hCG test ~~(see Section 8.4.1).~~</td><td>breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor. The subject must have a negative pregnancy test before restarting investigational product. If a subject'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 12.1.5 must also be followed.</td><td></td></tr>
<tr><td>Section 12.2.7
Laboratory Assessments</td><td>The list of laboratory analytes to be tested is shown in Table 1~~0~~.</td><td>The list of laboratory analytes to be tested is shown in Table 11, and the normal reference ranges for liver biochemistries are shown in Appendix C.</td><td>Added per Regulatory Authority request.</td></tr>
<tr><td>Section 12.2.7
Table 10 List of Laboratory Analytes</td><td><table><tr><td>~~Measurement of Liver Fibrosis~~</td><td>~~Fibroscan~~</td></tr><tr><td>~~Bone Density Assessment~~</td><td>~~DEXA~~</td></tr><tr><td>Other</td><td>Insertion</td></tr></table></td><td>Deletion<table><tr><td>Other</td><td>OCA-glucuronide</td></tr></table></td><td>Measurements of liver fibrosis are captured in a different section.

OCA-glucuronide was listed in the text but missing from the table.</td></tr>
<tr><td>Section 13
Statistical Methods</td><td>A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior ~~to study database lock~~, propensity score determination, and unblinding of the double-blind subject treatment assignments.</td><td>A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees prior to the first interim analysis, propensity score determination, and unblinding of the double-blind subject treatment assignments.</td><td>Reflects addition of interim analyses to the study protocol.</td></tr>
</table>

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
Section 13.1.1 Analysis Populations	~~• The Randomized Population will include all randomized subjects~~ ***Insertion***	***Deletion*** • **The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusion. Treatment assignment will be based on the randomized treatment.**	Rationale 12
Section 13.1.1.1 Comparability of Historical Controls	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria ~~where possible~~.	Historical controls from both databases will be chosen based on the same study inclusion/exclusion criteria. **Propensity score matching method will be utilized to select historical controls that match the treated subjects using available covariates. The adequacy of matching will be assessed by statistical methods described under Section 13.1.8**.	Clarifies the use of propensity scores in the assessment of the historical control population.
Section 13.1.2.1 Sample Size Monitoring	13.1.2.1 Sample Size ~~Re-Estimation Plan~~ Therefore, ~~starting approximately 2 years after the first subject is randomized,~~ the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of ~~121~~ adjudicated events for the final analysis in the combined groups. ~~If after 4 years of accruing subjects, despite increases in the number of subjects, it is determined that at least an additional 2 years (ie, total study duration of at least 10 years) are needed to randomize sufficient subjects to achieve a total of 121 adjudicated events, all subjects enrolled from that point forward will receive open-label OCA. Previously randomized subjects will~~	13.1.2.1 Sample Size **Monitoring** Therefore, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of subjects are required in order to obtain a total of **127** adjudicated events for the final analysis in the combined groups. ***Deletion***	Clarifies the ongoing monitoring of event rate and sample size.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~continue to be treated in a blinded manner with either OCA or matching placebo. If this modification is implemented, the alternative primary efficacy analysis is specified is Section 13.1.9.~~ ~~Any revised sample size or changes to treatment allocation will be justified and documented in a protocol amendment and in the CSR.~~		
Section 13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit	***Insertion (new subsection)***	**13.1.5.1 Association of Biochemistry with Clinical Outcomes and Clinical Benefit** **The association between biochemistry including ALP and bilirubin with clinical outcomes will be assessed and the clinical benefit of OCA using biochemistry as a surrogate endpoint will be evaluated. Detailed analysis will be described in the SAP.** **Based on the association between biochemical changes and clinical outcomes described above, clinical benefit of OCA using biochemistry as a surrogate endpoint for key subpopulations of interest will be evaluated. This analysis will be further described in the SAP.**	This analysis will provide additional insight into the connection between surrogate endpoints and clinical outcome events allowing for evaluation of benefit in subpopulations for which the study is not powered.
Section 13.1.8 Supportive Analysis	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment.	In order to address the risks associated with the inclusion of a long-term placebo arm, supportive analyses of the primary endpoint will compare clinical outcomes in the OCA treatment arm to historical controls, **which serves as an external control for supportive analysis**. By comparing how outcomes differ for treated subjects relative to historical controls, it is possible to estimate the effects of the treatment **between the treated subjects and the matched natural history subjects**.	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Although it might be relatively simple to assign a historical control based on a single observable characteristic, in practice, if the matching process is to successfully mitigate potential bias, it has to be done considering a~~ full range of covariates across which the treatment and historical controls might differ. Only covariates and not outcome variables will be included in the propensity score estimation. ~~Therefore, there is no chance of biasing,~~ to avoid biased results that are in favor of one treatment. The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	**A** full range of covariates across which the treatment and historical controls might differ **will be considered to mitigate potential bias**. Only covariates and not outcome variables will be included in the propensity score estimation **to avoid biased** results **that are** in favor of one treatment. **The baseline characteristics between treated and natural history subjects in the matched dataset will be summarized and presented in a tabular format. Statistical methods such as Wilcoxon Rank-Sum test will be used to assess the balance for baseline covariates. The standardized difference and variance ratios for these covariates will also be calculated. In addition, box plots of propensity scores for treated and natural history subjects will be separately presented, to further assess the adequacy of matching.** **A third-party statistician(s) will perform the propensity score modeling and matching. This third-party statistician(s) will be separate and independent from the statistician(s) who will assess the success of matching and perform efficacy analyses.** The propensity score quintile will be then be used as the stratification factor in the stratified log rank test to compare randomized OCA-treated subjects in the ITT population and historical controls (Overall Historical Control Population: both the UK-PBC Group and Global PBC Study Group databases) on the following outcomes:	Clarifies the use of the historical controls as an external control in supportive analyses of the primary endpoint and clarify the process for selecting the comparator group for the primary efficacy analysis using propensity score analysis.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	• ~~Time to hepatocellular carcinoma~~ ***(Text from Section 13.1.9 [Alternative Primary Analysis] modified and included in this section)*** ~~Based on sample size re-estimations, it may be determined that subjects will be enrolled to receive open-label OCA from that point forward, and the new~~ primary efficacy ~~analysis will become the comparison of~~ all subjects in OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause~~) (see Section 13.1.2.1~~). similar statistical methodology as specified above ~~in Section 13.1.8 for supportive analyses will be utilized~~. ~~The propensity score quintile will be then be used as the stratification factor in the stratified log-rank test to compare groups. 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 determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.~~ ~~In addition, the outcome events specified above in Section 13.1.8 will also be evaluated to compare all subjects in OCA population to all control subjects (randomized placebo and historical controls).~~ ~~Sensitivity analyses will be conducted limiting to the separate individual historical control databases, ie, UK-PBC Group and Global PBC~~	**Although the study is designed as a placebo-controlled study, the DMC may recommend changes to study conduct** based on **the pre-specified interim analyses (see Section 13.1.12), including the potential use of a revised** primary efficacy analysis. **This analysis would compare** all subjects in **the** OCA population, to all control subjects (randomized placebo and historical controls) on time to liver transplant or death (all-cause), **using** similar statistical methodology as specified above. **Notably, the planned primary analysis would not be revised without prior agreement with regulatory authorities.**	

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
	~~Study Group. To evaluate the robustness of the propensity score estimations, additional algorithms and factors may be considered.~~		
Section 13.1.9 Handling of Dropouts or Missing Data	***Insertion***	**In addition, the same analyses for primary and key secondary endpoints based on ITT and PP populations will be performed to assess robustness of analysis results. During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.**	Clarification of statistical analyses to address missing data.
Section 13.1.11 Examination of Subgroups	The primary and secondary efficacy endpoints will be analyzed for subject subgroups **(eg, age, sex, and race)** based on the ITT population. ***Insertion***	The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT population. **The primary efficacy endpoint will also be assessed across the spectrum of PBC disease stage as defined by Rotterdam criteria (Kuiper 2009)** • **Early (normal albumin and normal bilirubin)** • **Moderate (abnormal albumin or abnormal bilirubin)** • **Advanced (abnormal albumin and abnormal bilirubin)** **The primary efficacy endpoint will also be assessed for the following clinically relevant subpopulations.** • **Monotherapy in patients who are intolerant or non-responsive to UDCA** • **Elderly patients** **Assuming a strong correlation between biochemistry and clinical outcomes using the**	Added per Regulatory Authority request.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		total study population (Section 13.1.5.1) is observed, we will further assess the biochemical improvement in relevant subpopulations as applicable (eg, Rotterdam disease severity and monotherapy) and estimate the reduction in risk of clinical outcomes associated with the biochemical improvement. **Additional details regarding statistical methods and subgroup definitions will be provided in the SAP.**	
Section 13.1.12 Continuous Monitoring and Interim Analyses	***Insertion***	**13.1.12 Continuous Monitoring and Interim Analyses** **Blinded safety reports including the accrual of events, drop outs, and/or loss of subjects to commercially available OCA will be reviewed by the DMC on a regular basis.** **Two planned interim analyses of the liver-related outcomes will be conducted using the Lan-DeMets O'Brien-Fleming boundaries (Reboussin 2000). Both interim analyses will be pre-specified and will occur after accrual of 50% (64 events) and 75% (96 events) of clinical outcome events, respectively.** **The DMC will review the available efficacy data in conjunction with detailed safety data and other relevant information to recommend continuation, modification, or cessation (for efficacy) of the study beyond each interim analysis. Modification of the study would not take place without prior agreement with regulatory authorities.**	Two Interim Analyses have been added to the protocol.
Section 19 List of References	***Insertion***	**Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From**	Additional relevant references were added.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
		'cirrhosis' to 'cholangitis'. Digestive and Liver Disease. 2015a;47(11):924-6. **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Gastroenterology. 2015b;149(6):1627-9.** **Beuers U, Gershwin M, Gish R, et al. Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015c;62(5):1620-2.** **Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in Medicine. 1997;16(13):1515-1527.** **Pellicciari R, Fiorucci S, Camaioni E, et al. 6α-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-3572.** **Reboussin DM, DeMets, DL, Kim KM, et al. Computations for Group Sequential Boundaries Using the Lan-DeMets Spending Function Method. Controlled Clin Trials. 2000;21(3):190-207.**	
Appendix A Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment	Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability.	Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability **and biochemical response**.	Rationale 9
Appendix B	***This Appendix with the following information has been deleted.***		Redundant; Information is contained within the protocol.

Section	Original Text (Amendment 3, 07 September 2016)	Revised Text (Version 4, 10 May 2017)	Justification for Change
List of Study 747-302 Outcome Events	~~Several of the specified clinical endpoints will also by definition (see **12.1**) 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 12.1.4). 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~~		
Appendix C Reference Laboratory Values from Central Laboratories	***Insertion (new appendix)***	***Appendix containing reference laboratory values from central laboratories added.***	Added per Regulatory Authority request.

APPENDIX J. SUMMARY OF CHANGES: PROTOCOL VERSION 4 TO PROTOCOL VERSION 5 (DATED 04 JAN 2018)

Rationale

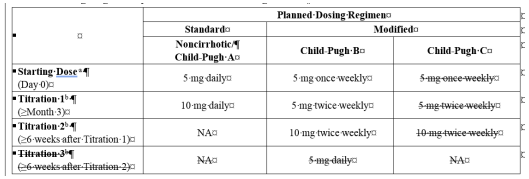
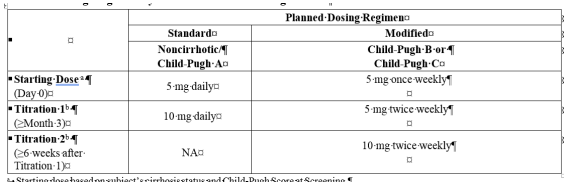
Protocol 747-302 was revised to include the following information:

- 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 United States Package Insert dosing guidelines. Titration is now only based on tolerability and not CP score.
- 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 diagnosed 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 5. Revised and new text in Version 5 is indicated in bold font, and the text deleted from Protocol Version 4 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below. Section numbers and names in column 1 refer to protocol Version 5 unless otherwise noted.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Sponsor's approval	PPD PhD PPD Clinical Development Intercept Pharmaceuticals, Inc.	PPD PhD PPD Clinical Development Intercept Pharmaceuticals, Inc.	Change in title
Study Personnel Contact Information	~~Contact: PPD MD, Medical Director, Drug Safety,~~ ~~Intercept Pharmaceuticals~~ ~~Mobile: PPD (Pacific time zone)~~ ~~Telephone: PPD~~ ~~Email: PPD~~	Primary Contact: PPD **MD, MPH|** **Senior Medical Director / Medical Affairs** **Syneos Health | Chapel Hill, NC 27514 |U.S.A.** **Tel:** PPD **Mobile:** PPD PPD **Secondary Contact:** PPD **DO, MSPH** **Senior Medical Director** **Intercept Pharmaceuticals, Inc. (Intercept)** PPD	Updated medical monitoring contact information
Synopsis, Phase of Development	Phase 4:	Phase 4: **US, Canada, and the EU** **Phase 3b: All other regions**	Clarified that the phase of the study has been changed from "3b" to "4" to reflect that this is a post-marketing 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.
Synopsis, Methodology,	…Subjects classified as Child-Pugh Class B ~~should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability and biochemical response.~~ ~~Subjects classified as~~ Child-Pugh Class C should	Subjects classified as Child-Pugh Class B or Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA **or** matching placebo twice weekly **(at least 3 days apart)**, based on tolerability and biochemical response.	To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly, based on tolerability and biochemical response		
Synopsis, Methodology, Table -Planned Dosing Regimen by Cirrhosis and Child-Pugh Score, Section 7.3, Planned Dosing Regimen, Table 3		 a Starting dose based on subject's cirrhosis status and Child-Pugh Score at Screening. b Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh Score at any time during the study c **Dosing per the twice weekly schedule must be at least 3 days apart**	Titration #3 is no longer applicable to study. To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Synopsis, Criteria for Evaluation; Secondary Objectives	Safety and tolerability Including the following: Treatment-emergent adverse events Clinical laboratory values	Safety and tolerability Including the following: Treatment-emergent adverse events **including adverse events of special interest** Clinical laboratory values	Per FDA request
Synopsis, Statistical Methods, Safety Analysis,	Safety data, including AEs, vitals, electrocardiogram	Safety data, including AEs, **AEs of special interest including pruritus and hepatic safety**, vitals, electrocardiogram…	Per FDA request
Section 5.1, Overview of Primary Biliary Cholangitis and Obeticholic Acid	In December 2016, the European Commission granted conditional approval for Ocaliva for the same indication	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 747-302 is considered a Phase 4 study in regions where OCA has received regulatory approval for PBC (ie, in**	Clarified that the phase of the study has been changed from "3b" to "4" to reflect that this is a post-marketing study in regions where OCA has received regulatory approval for PBC, ie, in the

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		the US, Canada, and the EU). In all other regions, this study is considered Phase 3b	US, Canada, and the EU. In all other regions, this study is considered Phase 3b
Section 5.4, Clinical Experience with Obeticholic Acid	As of ~~31 Jan~~ 2017, approximately ~~2186~~ subjects have received at least 1 dose of OCA. Of these, 844 were healthy volunteers, ~~525~~ subjects had PBC, ~~686~~ subjects had NASH, 41 subjects had diabetes mellitus/nonalcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and ~~52~~ subjects had primary sclerosing cholangitis, and ~~5~~ subjects 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** subjects had PBC, **1141** subjects had NASH, 41 subjects had diabetes mellitus/nonalcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and **73** subjects had primary sclerosing cholangitis, and **6** subjects had biliary atresia	Updated number of subjects exposed to OCA
Section 5.6, Importance of Monitoring of Disease Progression	Insertion	**Given PBC is a chronic, progressive liver disease, it is important that subjects with PBC are closely monitored to ensure early identification of potential disease progression to cirrhosis, decompensation and/or liver injury. More extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve subject oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules based laboratory monitoring. Subjects will be monitored for potential hepatic injury and/or decompensation and progression to cirrhosis (Section 7.5). Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 7.6 and Section 7.7. The more extensive monitoring is important given the elevated risk of**	Per FDA response

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		decompensation and potential for higher hepatic exposure to OCA in this population.	
Section 5.7, Summary of Known Potential Risks with OCA	…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, ~~but~~ with ~~a much lower~~ frequency ~~than that~~ observed in subjects 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 subjects 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 (HDL)~~ and an increase in low density lipoprotein (LDL). ~~Notably, in subjects 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,~~	**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. One case was reported in a subject with no evidence of cirrhosis at baseline, while the second case was reported in a subject with cirrhosis and hepatic impairment at baseline. 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)**	Per FDA Response Updated section to include SUSARS

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~decreases in total cholesterol were observed in subjects with PBC, while LDLc concentrations remained comparable to baseline and placebo in OCA treated subjects with the exception of a modest transient and early rise after initiation of treatment~~. Refer to the ~~Investigator's Brochure~~ (IB) for additional information regarding the known potential risks with the investigational product.	**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 providing further support for the lack of safety concern and positive benefit-risk profile of OCA.** **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.**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		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	
Table 1, Schedule of Procedures, Screening to Month 12	Insertion	**Added column for M2 and following procedures at the visit** • **Physical Exam** • **Child-Pugh Assessment** • **Adverse Events** • **Prior/Concomitant Medications** • **IP accountability/Compliance** • **Dosing Diary** • **Chemistry/Hematology/Coagulation** • **Review Progression to Cirrhosis Algorithm**	Added to satisfy requirement for monthly visits following any titration
	~~1 Month~~ Post-Titration Visit	Post-Titration Visit**s**	
Table 1, Schedule of Study Procedures, Screening to Month 12; and Table 2, Schedule of Study Procedures Year 2 Through End of Study	Insertions	Added the following procedures • **Gallbladder Assessment** *(Table 1 only)* • **Amylase and Lipase** (if subject experiences acute pancreatitis or cholecystitis) • **Review Progression to Cirrhosis Algorithm**	Added per FDA request

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Table 1, Schedule of Events, Screening to Month 12; and Table 2, Schedule of Study Procedures Year 2 Through End of Study	• ~~Assessments for Mayo Risk Score~~ • ~~DEXA~~ • ~~Blood samples for future analysis~~		Central lab will calculate value Procedures deleted to streamline collection of laboratory samples
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote b	Post-Titration visits must be performed 1 month (+ 1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child Pugh B and Child-Pugh C hepatic impairment. In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up titration to 10 mg OCA or matching placebo~~, or after ≥3 months at a decreased dose or frequency~~.	Post-Titration visits must be performed 1 month (+ 1 week) **and 2 months** (+1 week) after any up-titration in dose and/or frequency in subjects following modified dosing due to Child Pugh B and Child-Pugh C hepatic impairment. **See Appendix A for additional guidance.** In subjects following the standard dosing regimen, the post-titration visit must be performed **1 month (+ 1 week) and 2 months (+1 week)** only after the first up titration to 10 mg OCA or matching placebo.	Added to satisfy requirement for monthly visits following any titration
Table 1, Schedule of Study Procedures, Screening to Month 12, *previous* footnote f	~~Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the eCRF.~~	Deletion	MRS score will be calculated by central lab.
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote k	~~DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available. Please refer to Section 9.7.7 for additional information related to the allowed windows at Day 0 for this procedure~~	Deleted	Procedures deleted to streamline collection of laboratory samples

Section	Original Text (Amendment 4, 10 May 2017)		Revised Text (Version 5, 04 Jan 2018)		Justification for Change
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote k	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.~~		Ultrasound will be conducted to enhance HCC surveillance **and for gallbladder assessment at Screening. If ultrasound was not performed at Screening and the historic ultrasound is >3 months from Day 0, perform a hepatobiliary ultrasound at the Day 0 visit.**		Agreement with FDA to perform gallbladder assessments at screening.
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote p	The subject 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.		The subject 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. **MELD and MRS values will be calculated based on serum chemistry and coagulation values at each visit.**		MELD and MRS removed as line items. Central lab will calculate these values.
Table 1, Schedule of Study Procedures, Screening to Month 12, footnote l, Table 1, footnote w	~~Please refer to Section 11.1.2.3 for description of the blood sample to be collected for future analysis~~		Deletion		Procedures deleted to streamline collection of laboratory samples
Table 2, Schedule of Study Procedures Year 2 Through End of Study	Column header: ~~1 Month~~ Post-Titration Visit[a],		Post-Titration Visits[a]		Added to satisfy requirement for monthly visits following any titration, requirement to assess Child-Pugh at every visit.
Table 2, Schedule of Study Procedures Year 2 Through End of Study	~~Assessment for Mayo Risk Score~~[e] ~~DEXA~~ ~~Blood Sample for Future Analysis~~		Deletion		MRS score will be calculated by central lab.
Table 2, Schedule of Study	Visit Windows (+/-)c	Year 2 Through End of Study	Visit Windows (+/-)c	Year 2 Through End of Study	Added per FDA

Section	Original Text (Amendment 4, 10 May 2017)		Revised Text (Version 5, 04 Jan 2018)		Justification for Change
Procedures Year 2 Through End of Study	Insertion		**Amylase and Lipase**	**Sample to be collected if the subject experiences acute pancreatitis or cholecystitis**	
			Review Progression to Cirrhosis Algorithm		
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote a	~~In subjects following the standard dosing regimen, the post-titration visit must be performed only after the first up-titration to 10 mg OCA or matching placebo, or after ≥3 months at a decreased dose or frequency.~~ Post-~~titration visits~~ must be performed 1 month ~~±~~ 1 week after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment.		Post-**Titration Visits** must be performed 1 month **(**±1 week**) and 2 months (±1 week)** after any up-titration in dose and/or frequency in subjects following modified dosing due to Child-Pugh B and Child-Pugh C hepatic impairment. **See** Appendix A **for additional guidance. In subjects following the standard dosing regimen, the Post-Titration visit must only be performed 1 month (±1 week) and 2 months (±1 week) after the first up-titration to 10 mg OCA or matching placebo.**		Added to satisfy requirement for monthly visits following any titration, requirement to assess Child-Pugh at every visit.
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote e	~~Mayo Risk Score will be calculated based on central laboratory evaluations, diuretic use data, and peripheral edema assessment data captured in the CRF~~				MRS score will be calculated by central lab
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote g	~~Height will be collected at this visit~~				
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote j	~~DEXA will be conducted at 12-month intervals at all study sites where the DEXA device is available~~				Procedure deleted

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote m	The subject 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.	The subject 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. **MELD and MRS values will be calculated based on serum chemistry values at each visit.**	MELD and MRS removed as line items. Central lab will calculate these values.
Table 2, Schedule of Study Procedures Year 2 Through End of Study, footnote s	~~Please refer to Section for description of the blood sample to be collected for future analysis~~		Procedure deleted
Section 7.3, Planned Dosing Regimen	Insertion	**Non-Cirrhotic or Child-Pugh A** **…** **Cirrhotic or Child-Pugh B or C** **Subjects with cirrhosis (see Section 7.5.4) and classified as Child-Pugh Class B or Child-Pugh Class C will follow a modified dosing regimen, initiating 5 mg OCA or matching placebo once weekly. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria should up-titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly.** **Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).** **The dosing regimen should be determined as described shown in Table 13 Appendix A.**	Heading and text added for additional clarity.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		Investigators should follow the dosing/titration schedule as shown described in Section 7.4 and Appendix A.	
Section 7.3, Planned Dosing Regimen, Table 3	**Table 3: Changes in Dosing Regimen Due to Changes in Cirrhosis Status or Child-Pugh Score** **Original Status** / **New Status** **Noncirrhotic OR Child-Pugh A** — *No Change*; ~~10 mg daily → 5 mg daily~~ ~~5 mg daily → No change or~~ 10 mg twice weekly[b]; 5 mg or 10 mg daily → 10 mg twice weekly[b] **Child-Pugh B** — 5 mg daily → 10 mg daily; *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; ~~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*	**Table 3: Planned Dosing Regimen by Cirrhosis and Child-Pugh Score** **Scheduled Dosing Regimen**: **Standard** (**Noncirrhotic / Child-Pugh A**); **Modified** (**Child-Pugh B or Child-Pugh C**) **Starting Dose**[a] (Day 0): 5 mg daily; 5 mg once weekly **Titration 1**[b] (≥Month 3): 10 mg daily; 5 mg twice weekly[c] **Titration 2**[b] (≥6 weeks after Titration 1): NA; 10 mg twice weekly[c] [a] Starting dose based on subject's cirrhosis status and Child-Pugh score at Screening. [b] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status or Child-Pugh score at any time during the study (see Section 7.4). [c] Dosing per the twice weekly schedule must be at least 3 days apart.	To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Section 7.3, Planned Dosing Regimen, Table 4	~~**Table 4: Determination of Dosing Regimen**~~ ~~**Cirrhosis?** No Yes Yes Yes~~ ~~**Child-Pugh Score** Any A B C~~ ~~**Dosing Regimen** Standard Modified for Child-Pugh B Modified for Child-Pugh C~~	**Table deleted**	To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Section 7.4, Dose Titration Criteria	... Up-titrations may only occur to the maximum dose and frequency for each dosing regimen as defined in Section 7.3.	... Up-titrations may only occur to the maximum dose and frequency for each dosing regimen as defined in Section 7.3. **A 1-Month and 2 Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.7).**	Clarify dosing assessments.
Section 7.4, Dose Titration Criteria, Dose Titration due to Change in Cirrhosis or Child-Pugh Score	Changes to the dosing regimen ~~are not mandatory and should be based on clinical judgment as well as change in cirrhosis status. provides an overview of the possible changes in dosing regimen due to changes in cirrhosis or Child-Pugh Score~~. ... Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately	…Changes **in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and should not necessarily result in a change** to the dosing regimen ... Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters (**eg, increase in vitamin K resulting in**	Clarify that changes in CP scores should be discussed with medical monitor.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	and ~~should not necessarily result in~~ a change to the dosing regimen ~~Subjects who demonstrate an improvement in cirrhosis status or in Child-Pugh Score from B to A, or from Child-Pugh C to B, may be eligible to transition to the standard dosing regimen or the modified dosing for Child-Pugh B, respectively, based on tolerability. Prior to any dosing change, subjects must meet pre-titration assessment requirements for dosing as described in Section .~~ Child-Pugh Scores will be calculated at all quarterly study visits	**change in INR**) should be documented appropriately and **discussed with the Medical Monitor before any continuation** or change to the dosing regimen Child-Pugh Scores will be calculated **during screening**, at **each scheduled** study visits**, and at unscheduled visits in the event of signs or symptoms of suspected hepatic injury or decompensation are present.**	
Section 7.4.1, Pre-Titration Tolerability Assessment Requirements	Safety laboratory results obtained at the Month 1 visit (for titration at Month 3) or at the ~~1 Month~~ Post- Titration Assessment visit (for titration prior to or at the subsequent quarterly visit) are…	Safety laboratory results obtained at the visit (for titration at Month 3) or at the Post- Titration Assessment visit**s** (for titration prior to or at the subsequent quarterly visit) are…	Added to satisfy requirement for monthly visits following any titration

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.5, Monitoring and Management of Potential Hepatic Injury and/or Disease Progression	Insertion	**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 (Table 1). Child Pugh Scores should only be applied in patients who demonstrate progression to cirrhosis based on criteria presented in Section 7.5.4. 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 the assessments of signs and symptoms of hepatic injury and liver biochemistry, the investigational product may be interrupted or discontinued per criteria discussed in Section 7.5.2 and Section 7.5.3, and close monitoring procedures will be implemented (Section 7.7).**	Per FDA response, language added to provide guidance for monitoring disease progression due to potential hepatic decompensation.

Section 7.5.1, Signs and Symptoms of Hepatic Injury or Decompensation	Insertion	**7.5.1. Signs and Symptoms of Hepatic Injury or Decompensation** **Subjects 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 subject 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**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		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 7.5.2), (2) assessment of clinical events for potential hepatic decompensation (Section 7.5 (3) triggering of investigational product interruption or discontinuation per criteria (Section 8.4), (4) documentation in the AE eCRF or the SAE eCRFs (Section 12.1.5.1 and Section 12.1.5.2), and (5) contact with the Medical Monitor.**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.5.2, Liver Biochemistry Assessments for Suspected Hepatic Injury or Potential Hepatic Decompensation	Insertion	**Liver biochemistry will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of subjects for potential hepatic injury or hepatic decompensation. These assessments will be performed at:** • **Each protocol-specified visit** • **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 subject 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 subject evaluation (depending on the repeat result) are summarized in Table 5.** **Figure 2: DILI Management Algorithm.** **Table 5: 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**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

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		medical judgment. Investigators will be reminded to be cautious and mindful in their evaluation of subjects' 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.	
Section 7.5.3, Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events	Insertion	**Subjects will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for the monitoring these events and the interruption/discontinuation of investigational product is summarized in Table 6.** **Investigational product should be discontinued permanently if the subject received a liver transplant or experiences multi-organ failure as defined in Table 6, Part A). Subjects should continue to return for scheduled study visits for safety follow up.** **Subjects who experience other potential hepatic decompensation events defined in Table 6, Part B should be closely monitored until normalization or stabilization. Subjects may be rechallenged after a minimum of 30 days if fully resolved OR stable and approved by the Medical Monitor and Investigator.** **Table 6: Criteria for Monitoring Potential Hepatic Decompensation Events and Interruption / Discontinuation of Investigational Product**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation
Section 7.5.4, Assessing Cirrhosis		*Section and subsections were moved from previous Section 9.7.3 and subsections.*	Content moved as it supports new content described above.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.5.5, Child-Pugh Score		*Section was moved from previous Section 9.7.4.*	
Section 7.5.5.1, Mayo Risk Score		*Section was moved from previous Section 9.7.5.*	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 7.6, Dose Adjustment, Interruption, and Withdrawal from Investigational Product or Study	Insertion	**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 8), investigational product should be initiated at a lower dose and subjects 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 8. Subjects that 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 terminate at the time when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Table 8, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination.** **Table 8: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge.**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

Section 7.7, Close Observation	Insertion	**If investigational product is interrupted or discontinued as described in Section 7.6, subjects 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 subject 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 subject 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 subject 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 7.5.1, Section 7.5.2, and Section 7.5.3. These cases need to be discussed with the Sponsor's medical monitor:** • **Repeating liver enzyme and serum bilirubin tests as described in Section 7.5.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic, as clinically indicated.**	Per FDA response, added to provide guidance for monitoring disease progression due to potential hepatic decompensation

		• **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 subject 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 (HEV) when assessing for hepatic decompensation as infection with HEV 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**	

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Section 8.4. Subject Withdrawal Criteria	~~Investigational product may be temporarily decreased (eg, from 10 mg to 5 mg daily, or by decreasing dosing frequency) or temporarily or permanently stopped based on tolerability concerns. The dose of investigational product should be adjusted back to the maintenance dose in a blinded manner once the issues relating to the lack of tolerability are resolved.~~ ~~Subjects that 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 when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Section 8.4.1, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination~~.	**Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from** investigational product are expected to continue in the study and **should** follow the regular visit schedule **for the duration** of the study**. See Section 7.6 for withdrawal criteria related to potential hepatic injury and/or decompensation; including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.1 below.**	Section updated to conform with FDA response.
Previous Section 8.4.1.1, Reasons for Additional Monitoring Related to Liver Chemistries (Version 4)	~~Subjects 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. Subjects with persistent elevations (eg, additional lab testing per Investigator discretion) should be closely monitored. Concomitant elevations in total bilirubin or international normalized ratio (INR) with persistent increases in ALT or AST should also be closely monitored~~		Replaced with updated DILI text in Section 7.5.
Previous Section 8.4.1.2, Reasons for Investigational	~~Development of any of the following clinical laboratory values, without explanation, during the~~		Replaced with updated DILI text in Section 7.5.

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Product Interruption Related to Elevated Liver Chemistries (Version 4)	~~study mandates investigational product interruption:~~ ~~• AST and/or ALT >3x baseline (and >ULN)~~ ~~• Total bilirubin >2x 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 AE information should also be collected and the subject 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 >3x baseline (and >ULN) or total bilirubin >2x baseline (and >ULN), subjects 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 study medication and no other cause for the elevation is identified, it may be assumed that the elevations were due to disease progression and the subject may be re-challenged following a~~		

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~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.~~ ~~If at any time a subject 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.~~ ~~Subjects who develop evidence of severe drug-induced liver injury, which 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,~~		

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~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 subjects 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 subject to continue treatment. In the event the investigational product is required to be discontinued, subjects should be encouraged to continue study visits for continued data collection but may withdraw consent at any time.~~ ~~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 13.4)~~		
Previous Section 8.4.1.3,Pregnancy (Version 4)	~~If a female subject becomes pregnant, she must interrupt treatment with investigational product immediately, but should continue with the study visit schedule. As described in Section 12.1.11 pregnancy is not considered an AE for reporting purposes. The subject may re-start 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 12.1.11.~~		Addressed in Table 8 in Section 7.6.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Previous Section 8.4.2.1, Liver Transplantation (Version 4)	~~Subjects who undergo a liver transplant during the course of the study must discontinue investigational product and discontinue the study visit schedule. However, these subjects 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 discussed in Table 8 in Section 7.6
Section 9.7.1, Visit Windows	Post-Titration Visit: 1 month (+1week [7 days]) from date of titration ~~or after ≥3 months at a decreased dose or frequency~~	Post-Titration Visit: 1 month **and 2 months** (±1week [7 days]) from date of titration	Added to satisfy requirement for monthly visits following any titration
Previous 9.7.3, Assessing Cirrhosis (Version 4)		*Section and subsections were moved to earlier in the document (7.5.4 and subsections).*	Content moved.
Section 9.7.3, Screening Procedures (1 to 8 Weeks prior to Day 0)	**…** • ~~Perform assessment for calculation of Mayo Risk Score~~ • 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 Visit 2~~, and a report/adequate data are available, a pretreatment ultrasound at ~~Screening Visit 2~~ is not required. … Results from the screening ultrasound ~~should~~ be reviewed to assess possible exclusion criteria prior to randomization. • ~~Record current~~ concomitant medications • ~~In preparation for the dual-emission X-ray absorptiometry (DEXA) bone~~	… • Perform an ultrasound for HCC surveillance and **gallbladder assessment** (if equipment is unavailable, sites should make every attempt to use available community referral sites). If an ultrasound has been done within **3** months **of the planned Day 0 visit**, and a report/adequate data are available, a pretreatment ultrasound is not required. … Results from the screening ultrasound **must** be reviewed to assess possible exclusion criteria, prior to randomization. • **Review and record prior and** concomitant medications	Agreement with FDA to perform gallbladder assessments at screening.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~density scan to be done at Day 0 (at all study sites where the device is available), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.~~		DEXA removed to streamline laboratory procedures.
Previous Section 9.7.4, Child-Pugh Score (Version 4)		*Section was moved to earlier in the document (7.5.5).*	Content moved.
Section 9.7.4, Day 0 Procedures (Randomization)	… ~~Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable. If DEXA has been done within 12 months of Day 0 and a report/adequate data are available, a pretreatment DEXA at Day 0 is not required. If the DEXA cannot be performed on Day 0 (eg, device/technician unavailability, scheduling issues, etc), the procedure may be completed within the screening visit window, as close as possible to the Day 0 visit, preferably, after subject eligibility has been confirmed~~. … • Obtain blood samples for: – OCA, C4, and fibroblast growth factor-19 (FGF-19)	**…** • **If hepatobiliary ultrasound for HCC screening and gallbladder assessment was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound.** … Obtain blood samples for: – OCA, C4, and fibroblast growth factor-19 (FGF-19)	Per FDA request

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	– Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF]) – Genetics (see Section 11.1.2.3) ~~– Blood sample for future analysis (refer to Section 11.1.2.3)~~	– Markers of hepatic fibrosis and/or inflammation (including enhanced liver fibrosis [ELF]) – Genetics (see Section 11.1.2.3) • **Perform assessments for calculation of Child-Pugh Score**	
Previous Section 9.7.5, Mayo Risk Score (Version 4)		*Section was moved to earlier in the document (7.5.5.1).*	Content moved.
Section 9.7.5, Month**s** 1**, 2** Procedures	… • Review and record concomitant medications. … In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 visit laboratory requirements: -At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the ~~Month 1~~ visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;	… • Review and record **prior and** concomitant medications. … • **Perform assessments for calculation of Child-Pugh Score.** • **Review progression to cirrhosis algorithm.** … In the event it is not feasible for the subject to return to the site for the above referenced procedures, the following alternative visit procedures are available to help ensure compliance with the Month 1 **and Month 2** visit laboratory requirements: -At the Day 0 visit, the subject can be provided with the central laboratory collection kit and shipping materials associated with the Month 1 visit, and have the laboratory specimen collection performed at his or her local doctor's office or designated laboratory collection center. The subject must also be contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -If all other options for the collection of the Month 1 **and Month 2** laboratory samples have been	Month 2 added to section satisfy requirement for monthly visits following any titration and assess CP score per FDA request.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	-If all other options for the collection of the Month 1 laboratory samples have been exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. The subject must also be contacted via telephone at the ~~Month 1~~ visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -A physical examination should be performed at the Month 3 visit if an onsite Month 1 visit was not performed.	exhausted, the use of a local laboratory for the Month 1 samples would be accepted for this visit; although, any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. **The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern.** The subject must also be contacted via telephone at the visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance; -A physical examination should be performed at the Month 3 visit if an onsite Month 1 **or Month 2** visit was not performed.	
Section 9.7.6 Month 3 Procedures;	Insertions.	… • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications.	Per FDA request
Section 9.7.7, Post-Titration Visit Procedures	… • Review and record concomitant medications. … If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the	… • Review and record **prior and** concomitant medications. **…** • **Perform assessments for calculation of Child-Pugh Score.** • **Review progression to cirrhosis algorithm.** **…** If all other options for the collection of the Post-Titration laboratory samples have been exhausted, the use of a local laboratory for the Post-Titration samples would be accepted for this visit; although,	per FDA request

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	Post-Titration samples would be accepted for this visit although any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the investigator for review and available in the source records. The subject must also be contacted via telephone at the Post-Titration Visit time point to assess AEs, review concomitant medications, and assess investigational product compliance;	any laboratory data obtained from a local laboratory will not be captured in the eCRF or included in the study analysis. A copy of the local laboratory report would need to be provided to the Investigator for review and available in the source records. **The Investigator should contact the Medical Monitor as soon as possible to discuss any local laboratory values that may be of clinical concern.** The subject must also be contacted via telephone at the Post-Titration Visit timepoint to assess AEs, review concomitant medications, and assess investigational product compliance;	
Section 9.7.8, Month 6 Procedures	… • ~~Perform assessment for calculation of Mayo Risk Score.~~ … • Review and record concomitant medications. … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – ~~Blood sample for future analysis (refer to Section 11.1.2.2)~~	… • **Review progression to cirrhosis algorithm.** **…** • Review and record **prior and** concomitant medications. … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF)	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 9.7.9 Month 9 Procedures	… • Review and record concomitant medications … • ~~In preparation for the DEXA bone density scan to be done at the Month 12 visit (at all study sites where the device is available), subjects who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan~~	… • **Review progression to cirrhosis algorithm** • Review and record **prior and** concomitant medications …	per FDA request. Procedure deleted.
Section 9.7.11 Month 12 Procedures	… ~~Perform assessment for calculation of Mayo Risk Score.~~ … • ~~Conduct a DEXA bone density scan (at all study sites, where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable~~ … • Review and record concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3) ~~Blood sample for future analysis (refer to Section 11.1.2.3)~~	**…** • **Perform assessments for calculation of Child-Pugh Score** • **Review progression to cirrhosis algorithm** **…** • Review and record **prior and** concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3)	Per FDA request. Procedures deleted.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 9.7.12, Month 3 and Month 9 Continued Follow-Up Procedures (±2 weeks)	Insertions	… • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications	
Section 9.7.13, Month 6 Continued Follow-Up Procedures (Semi-annually [±2 weeks])	• ~~Perform assessment for calculation of Mayo Risk Score.~~ • Perform assessments for calculation of Child-Pugh Score. … • Review and record concomitant medications … • Obtain blood samples for: – Markers of hepatic fibrosis and/or inflammation (including ELF). – ~~Blood sample for future analysis (refer to Section 11.1.2.3).~~ • ~~At the semi-annual visit, in preparation for the DEXA bone density scan to be done at the annual visit (at all study sites where the device is available), subjects~~	• Perform assessments for calculation of Child-Pugh Score. • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications … • Obtain blood samples for: – Markers of hepatic fibrosis and/or inflammation (including ELF).	per FDA request. Procedures deleted

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~who are taking calcium supplements should stop taking them for 48 hours before the scan. If the subject is taking any medications for osteoporosis or osteopenia, s/he should not take them on the day of the scan.~~		
Section 9.7.14, Month 12 Continued Follow-up Procedures (Annually [±2 weeks])	• ~~Perform assessment for calculation of Mayo Risk Score~~ … • ~~Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable~~. … • Review and record concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3) – ~~Blood sample for future analysis (refer to Section 11.1.2.3~~	**…** • **Review progression to cirrhosis algorithm** … • Review and record **prior and** concomitant medications … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) – Genetics (see Section 11.1.2.3)	per FDA request. Procedures deleted

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 9.7.15, Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent	Table 9, footnote c … ~~No~~ Additional data (~~e.g. AE~~, concomitant ~~medication, etc) data will~~ be collected, ~~except as indicated in Section~~ . Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing. … • ~~Perform assessment for calculation of Mayo Risk Score~~ … • ~~Conduct a DEXA bone density scan (at all study sites where the device is available); document whether the subject stopped taking her/his calcium supplements for 48 hours before the scan and medications for osteoporosis or osteopenia on the day of the scan, if applicable.~~ • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF) • ~~Blood sample for future analysis (refer to Section 11.1.2.3~~	Table 9, footnote c … Additional data **such information on concurrent medical conditions, co-morbidities, relevant and** concomitant **medications may** be collected **to help facilitate adjudication of these post-study events.** Some assessments noted below may be omitted if they have been completed within the 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing. … • **Review progression to cirrhosis algorithm** … • Obtain blood samples for: – OCA, C4, and FGF-19 – Markers of hepatic fibrosis and/or inflammation (including ELF)	
Section 11.1.2.3, Other Exploratory Evaluations	• ~~Blood samples for future analysis of additional analytes, such as PBC autoantibodies and other cytokines and interleukins, may be assayed on an exploratory research basis. Blood samples may also be used to assess other disease or investigational product characteristics. Appropriate serum and plasma samples will be collected at selected time points during the study. Subjects will be permitted to decline future~~	Deleted	Procedure deleted

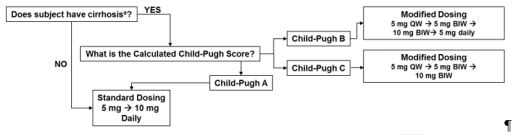
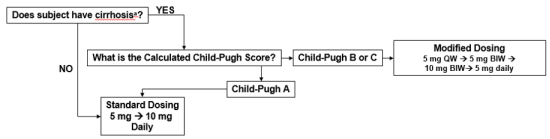
Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
	~~analysis of blood samples without affecting their involvement in the study. IRB/IEC review and approval will be required and willing subjects must specifically consent to participate in this evaluation. The samples will be stored for up to 1 year after the end of the study and destroyed after 1 year if not analyzed.~~		
Section 12.1.1.1, Adverse Event	Insertions	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) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. **For reporting purposes, pregnancy is not considered an AE** **Subjects 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 the or whites of eyes, and bruising easily.**	Per FDA request
Section 12.1.1.4, Adverse Events of Special Interest	Insertion	**The following decompensation events are adverse events of special interest. A subset of these events are also individual components of the primary endpoint (Section 11.1.1).** • **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, irrespective of hospitalization or requirement of blood transfusion.**	Per FDA request

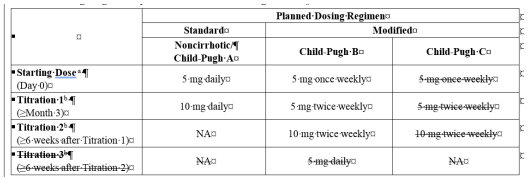
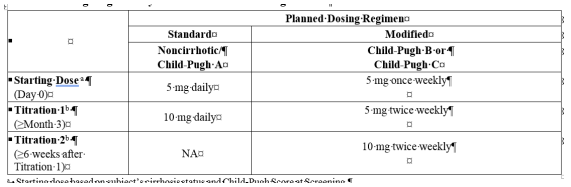
Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		• **Gastrointestinal bleeding as a result of gastric or duodenal varices verified by endoscopy** • **Hepatic encephalopathy, Grade ≥2** • **New onset ascites requiring treatment** • **Worsening 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	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Section 12.1.5.1, 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 subject.**	Per FDA request
Section 12.1.10, Follow-up of AEs and SAEs	… Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results should be recorded in the CRF. Note that longer follow-up can sometimes reveal an off-drug repetition.	**Drug-Induced Liver Injury or Disease Progression** … Drug-induced liver injury may develop or progress even after the causative drug has been stopped. Results **from drug induced liver injury follow-up** should be recorded in the **e**CRF. Note that longer follow-up can sometimes reveal an off-drug repetition… **Cholecystitis or Pancreatitis** **At the time of consent for new subjects (or re-consent to the protocol amendments for ongoing subjects), subjects will 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. Subjects will 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 will be instructed to promptly bring subjects 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)**	

Section	Original Text (Amendment 4, 10 May 2017)		Revised Text (Version 5, 04 Jan 2018)		Justification for Change
			• **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 will be monitored monthly for 3 months after onset of symptoms, irrespective of whether a diagnosis of cholecystitis and or pancreatitis is confirmed. Results should be recorded promptly in the eCRF.**		
Section 12.2.5, Dual Emission X-Ray Absorptiometry	~~12.2.5. Dual Emission X-Ray Absorptiometry~~ ~~A bone density assessment will be done using the DEXA scan.~~		Deleted		Procedure deleted
Section 12.2.6, Laboratory Assessments	Subjects will be instructed to attend ~~each of~~ their study visits (except Screening) in a fasted state,		Subjects will be instructed to attend **any** study or **unscheduled laboratory** visits (except Screening) in a fasted state,		Clarify subject should fast for all lab visits.
Section 12.2.6, Laboratory Assessments, Table 13	Laboratory Assessment	Analyte	Laboratory Assessment	Analyte	Labs added per FDA request
			Markers of Cholecystitis and Pancreatitis	**amylase and lipase**	
	~~Blood Sample for Future Analysis~~	~~PBC autoantibodies and other cytokines and interleukins TBD~~			Procedure deleted
Section 12.2.6, Laboratory Assessments,	MELD scores, Child-Pugh score, ~~and MRS~~ will be calculated at screening, and ~~at quarterly (MELD and Child-Pugh scores) or semi-annual (MRS)~~ visits based on serum chemistry and coagulation.		MELD scores **and** Child-Pugh score will be calculated at screening, and at **all** visits based on serum chemistry and coagulation.		Clarify subject should fast for all lab visits
Section 13.2.1, Safety Analyses, Adverse Events	Insertion		**Adverse events of special interest as described in Section 12.1.1.4 will be summarized for each treatment group. In addition, each event is a**		Per FDA request.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		component of the primary endpoint, and will be summarized as secondary endpoints as described in Section 13.1.4.	
Section 13.4, Adjudication Committees	All suspected liver-related clinical outcomes, 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,	All suspected liver-related clinical outcomes and MACE/Expanded MACE 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 **2** 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 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,	There is no longer a need for the Hepatic Safety Committee given the updated guidance for the Investigator.
References		**Kumar A, Saraswat V. Hepatitis E and Acute-on-Chronic Liver Failure. J Clin Exp Hepatol. 2013 Sep;3(3):225-30. doi: 10.1016/j.jceh.2013.08.013. Epub 2013 Sep 16** **Banks O, Bollen T, Dervenis C, et al. Classification of acute pancreatitis02012: revision of the Atlanta classification and definitions by international consensus. Gut.2013;62:102-111.**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
		Greenburg J, Hsu J, Bawazeer M., et al. Clinical Practice Guideline: Management of acute pancreatitis. Can J Surg. 2016;59 (2):128-140. **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.**	
Appendix A, Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment	… ~~Overview of Modified Dosing Regimen for Subjects with Child-Pugh B or C Hepatic Impairment~~ ~~An overview of the modified dosing regimen for subjects with Child-Pugh Class B or Child-Pugh Class C is presented in and .~~ ~~Subjects who are cirrhotic and classified as Child-Pugh Class B or Child-Pugh Class C will initiate a modified treatment regimen with 5 mg OCA or matching placebo once weekly for at least 3 months. Subjects classified as Child-Pugh Class B should eventually titrate to a maximum dose of 5 mg OCA or matching placebo once daily, based on tolerability and biochemical response. Subjects classified as Child-Pugh Class C should titrate to a maximum dose and frequency of 10 mg OCA or matching placebo twice weekly.~~	**Subjects with cirrhosis and classified as Child-Pugh B or Child-Pugh C at Screening will follow a modified dosing schedule initiating 5 mg OCA or matching placebo once weekly as described in Figure 3. After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least three days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up titrate to the maximum allowed dose of 10 mg OCA or matching placebo twice weekly (Table 14). Investigators may decrease the dosing frequency (back to once weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).**	Deleted overview section and replaced with text
Appendix A, Figure 3	 *'Cirrhosis may be assessed by histology or non-histological methods as defined in Section 9.7.3. BIW = twice weekly; QW = once weekly	 *'Cirrhosis may be assessed by histology or non-histological methods as defined in Section 7.5.4. BIW = twice weekly; QW = once weekly	Same dosing scheme for CP-B and CP-C subjects.

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Appendix A, Table 14			Titration #3 is no longer applicable to study. To align with label, maximum dose for Child-Pugh B or C subjects is 10 mg OCA twice weekly.
Appendix A	~~Modified Dosing Regimen for Subjects with Child-Pugh B Hepatic Impairment~~ ~~Subjects with cirrhosis and classified as Child-Pugh BC at Screening will follow a modified dosing schedule receiving 5 mg OCA or matching placebo once weekly as described in . After a minimum of 3 months dosing once weekly with 5 mg OCA or matching placebo, and following review of the pre-titration laboratory results to assess safety and tolerability, the dosing frequency of 5 mg OCA or matching placebo should be increased to twice weekly (at least 3 days apart). Subjects who have maintained the twice weekly dosing frequency for a minimum of at least 6 weeks, and meet the dose titration criteria, should up-titrate to twice weekly dosing with 10 mg OCA or matching placebo. Subjects with at least 6 weeks of twice weekly dosing at 10 mg OCA or matching placebo, and meeting dose titration criteria, should up-titrate to the maximum allowed dose of 5 mg OCA or matching placebo once daily.~~ ~~Investigators may decrease the dosing frequency (back to once or twice weekly) or dose for any subject at any time during the study, as considered clinically appropriate (eg, tolerability).~~		
Appendix A, Dose Titration due to Change in	~~Subjects on a modified dosing regimen who~~ demonstrate a change in cirrhosis status 7.5.4 ~~and~~/or Child-Pugh Score7.5.5 should ~~have their dose of investigational product modified to match~~	**When subjects** demonstrate a change in cirrhosis status (**as assessed per Section 7.5.4)** or Child-Pugh Score (**Section 7.5.5 dosing** should **be reassessed and** the dosing regimen **modified appropriately**.	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Cirrhosis or Child-Pugh Score	~~their current status per the appropriate dosing regimen (see Section ,)~~; ~~however, changes to~~ the dosing regimen ~~are not mandatory and should be based on clinical judgment as well as changes in status~~. Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters should be documented appropriately, and ~~should not necessarily result in~~ a change to the dosing regimen. ~~Investigators may contact the Medical Monitor at any time to discuss potential changes to dosing.~~ Possible scenarios for dosing modifications include: • Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C • Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study ~~• Improvement in classification of Child-Pugh Score from C to B~~ ~~• Improvement in classification of Child-Pugh Score from B to A; these subjects may be eligible to transition to the standard dosing regimen~~ Subjects may titrate dose and dosing frequency up or down as appropriate, within the ~~appropriate~~ dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.10).	Changes in Child-Pugh Score that result from a transient, explainable change in laboratory parameters **(eg, increase in INR due to vitamin K deficiency)** should be documented appropriately and **discussed with the Medical Monitor before any continuation** or change to the dosing regimen. Possible scenarios for dosing modifications include: • Subjects who develop cirrhosis during the course of the trial with a classification of Child-Pugh B or C • Subjects with pre-existing cirrhosis who demonstrate a change in the Child-Pugh Score from A to B or C at any point in the study Subjects may titrate dose and dosing frequency up or down as appropriate, within the dosing regimen. Up-titration should be done per Investigator discretion and be guided by the pre-titration tolerability assessments outlined in Section 7.4.1. A 1-**Month and 2**-Month Post-Titration Assessment must be performed any time a subject's dose or frequency is up-titrated (see Section 7.1.2 and Section 9.7.7).	
Appendix A, Unscheduled	…: The ~~+~~ 1 week window ~~week~~ related to the ~~1~~ month Post-Titration Visit can be ~~extended for~~ ~~up~~ to ~~an additional~~ 5 weeks to allow for the post-	…: The ±1 week window related to the **2**-month Post-Titration Visit can be **modified** to **occur 2** weeks **earlier or 2 weeks outside of the allowed**	

Section	Original Text (Amendment 4, 10 May 2017)	Revised Text (Version 5, 04 Jan 2018)	Justification for Change
Titration Visit, Optional Visit	titration assessment to be performed during one of the subject's regularly scheduled study visits. If the ~~window~~ ~~is extended past +1 week allowed~~ visit ~~window, at a minimum, a telephone safety contact~~ should ~~then~~ be performed ~~1 month post-titration.~~	**visit window** to allow for the post-titration assessment to be performed during one of the subject's regularly scheduled study visits. If the 2-**month Post-Titration Visit** is **performed during a regularly scheduled study** visit, **all scheduled procedures associated with that visit** should be performed.	

APPENDIX K. SUMMARY OF CHANGES: PROTOCOL VERSION 5 TO PROTOCOL VERSION 6 (DATED 05 NOV 2019)

Rationale

Protocol 747-302 was revised as follows:

- Updated contraception language to align with CTFG guidelines for highly effective methods
- Updated the section on the total number of subjects exposed to OCA as of 26 May 2019
- Update the section on known potential risks of OCA
- Updated the section on reporting of adverse events to include instructions for reporting SUSARs
- Included various options for retaining subjects in the study and emphasized the critical importance of collecting clinical outcomes data
- Provided guidance for Investigators on the importance of documenting specific reasons in the EDC for subjects who discontinue treatment and/or the study, especially for subjects who discontinue due to adverse events
- Provided guidance for Investigators on study procedures for subjects who reconsent to participate in the study

Summary of Changes

The following revisions were made to the protocol in Protocol Version 6. Revised and new text in Version 6 is indicated in bold font, and the text deleted from Protocol Version 5 is crossed out in the table below. Minor/editorial changes are not listed individually in the summary table below. Section numbers and names in column 1 refer to protocol Version 6 unless otherwise noted.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
STUDY PERSONNEL CONTACT INFORMATION, Secondary Contact	PPD ~~DO, MSPH~~ ~~Senior Medical Director~~ ~~Intercept Pharmaceuticals, Inc. (Intercept)~~ PPD	PPD **MD| Executive Director, Clinical Research** **Intercept Pharmaceuticals, Inc. (Intercept)| New York, NY 10001** **Tel:** PPD **Mobile:** PPD PPD	Change in the Sponsor's medical director.
Synopsis, Methodology	This Phase 4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC.	This Phase **3b**/4, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC.	Revision was made to clarify that in the US, Canada and Europe, this study is being conducted as a phase 4 study. In all other regions, it is a phase 3b study.
Synopsis, Methodology	New language added.	**With the exception of liver transplant, if a subject experiences a suspected or confirmed clinical outcomes event, the subject should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for discontinuation outlined in the protocol. Subjects who discontinue investigational product are expected to be followed through to study closure (or at the discretion of the Sponsor). Additional information regarding subject follow-up and different options available to subjects is provided in Section 7.9 and Section 8.4.**	Clarification of study procedures for subjects who discontinue treatment.
Synopsis, Diagnosis and Main Criteria for Inclusion, Inclusion Criteria	5. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective	5. Contraception: Female subjects **must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥1 highly effective method of contraception** during the study and for 30 days **after the end of treatment**. **Highly effective methods of contraception per the CTFG guidelines are those that alone or in combination results in a failure rate of less than 1% per year when**	Inclusion criterion #5 was updated per CTFG guidelines for highly effective

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
	methods of contraception are considered to be those listed below: • ~~Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~ • Intrauterine device (IUD) • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection) • Abstinence, if in line with the preferred and usual lifestyle of the subject	**used consistently and correctly. Highly effective methods of contraception are as follows:** • Intrauterine device - Intrauterine device (IUD) - **Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • Vasectomy (partner) • **Combined (estrogen and progestogen containing) hormonal contraception (eg, oral, intravaginal or transdermal) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.** • **Progestogen-only hormonal contraception (eg oral, injectable or implantable) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.** • **Sexual** abstinence, if in line with the preferred and usual lifestyle of the subject **(where abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).**	methods of contraception within a clinical study.
Synopsis, Exclusion Criteria	5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions ~~such as chronic lymphocytic leukemia~~)	5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions)	Revised to remove chronic lymphocytic leukemia as a benign medical condition.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
Synopsis, Duration of Treatment	~~It is expected that subjects will be followed up for a minimum of 6 years.~~ The study is event driven and total duration ~~of treatment~~ will be determined by the time to accrue 127 ~~total~~ primary endpoint events.	The study is event driven and total duration will be determined by the time **required** to accrue **approximately** 127 primary endpoint events**, estimated to be approximately 10 years. Subjects are expected to have a minimum follow-up time of approximately 6 years.**	Updated the estimated study duration.
5.4, Clinical Experience with Obeticholic Acid	As of ~~13 Oct 2017~~, approximately ~~2690~~ subjects[1] have received at least 1 dose of OCA. ~~Of these, 844 were healthy volunteers, 552 subjects had PBC, 1141 subjects had NASH, 41 subjects had diabetes mellitus/nonalcoholic fatty liver disease, 33 subjects had alcoholic cirrhosis/portal hypertension, and 73 subjects had primary sclerosing cholangitis, and 6 subjects had biliary atresia.~~ ~~[1] Includes estimated numbers from ongoing blinded studies~~	As of **26 May 2019**, approximately **5386** subjects have **been enrolled in the clinical development program for OCA.** Approximately **3926** subjects have received at least 1 dose of OCA **in completed and ongoing clinical trials**.	Updated the number of subjects exposed to OCA as of 26 May 2019.
5.4, Clinical Experience with Obeticholic Acid	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. The LTSE phase of ~~studies 747-201 and~~ 747-301 ~~are~~ ongoing; the LTSE phase of Study 747-202 ~~is~~ complete.	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. The LTSE phase of **Study** 747-301 **is** ongoing; **(a final CSR is pending);** the LTSE **phases** of Study 747-**201 and Study 747-**202 **are** complete.	Updated the status of clinical studies in PBC.
5.5.1 Rationale for Study Design	Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis	Study 747-302 is a clinical outcomes study, supportive of Phase 3 Study 747-301 which was based on a surrogate biochemical endpoint, designed to confirm the clinical benefit of OCA treatment in patients with PBC. A retrospective observational database (Global PBC Study Group [Lammers 2013]) of patients with PBC allowed for a rigorous patient-level meta-analysis and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study. **Despite the observational evidence that links ALP and**	Added language to stress the importance of collecting clinical outcomes data.

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	and provided an opportunity for a robust assessment of ALP and bilirubin as viable surrogate biochemical parameters and a comprehensive understanding of the natural history of the PBC disease process. Data from the Global PBC Study Group was also utilized to inform the design of the confirmatory outcomes study.	**bilirubin to clinical outcomes in PBC, it is necessary to prospectively validate these surrogate endpoints. As such collecting outcome information in Study 747-302 is of the utmost importance.**	
5.7. Summary of Known Potential Risks with OCA	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	Clinical Data In two Phase 2 studies and a Phase 3 study evaluating OCA in the treatment of subjects with PBC, hepatic adverse events, **including jaundice, worsening ascites and primary biliary cholangitis flare,** 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), **as early as one month after starting treatment with OCA**. **In addition,** 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. 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 individual subject and aggregate data **from both** the Phase 3 clinical outcomes study in subjects with PBC (Study 747-302) and the Phase 3 pivotal **studies in subjects** with NASH fibrosis (Study 747-303) **and NASH cirrhosis (Study 747-304) on a quarterly basis, in an unblinded fashion, and in**	Updated the known potential risks of OCA.

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	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	**closed sessions (without the Sponsor's participation). In the quarterly DMC meetings to date, the DMC has recommended** the studies continue without modification. **Following a request from the FDA to provide an up to date DMC report analyzing unblinded data on respective incidence of cholecystitis, cholelithiasis, and pancreatitis by treatment group across all ongoing clinical studies, an ad hoc DMC review was held and the DMC recommended that:** • **As it concerned pancreatitis, all studies continue without changes.** • **For subjects in Study 747-303, investigational product should be uninterrupted in subjects who experience symptomatic cholelithiasis and/or cholecystitis.** **The Sponsor implemented the DMC recommendations across the NASH program but not the PBC program.** Post-Marketing Cases in PBC As of **26 May 2019,** the **estimated cumulative patient exposure from** marketing **experience is 7694 patient-years.** 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.	

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	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.	Refer to the **current version of the OCA Investigator's Brochure** for additional information regarding the known potential risks with the investigational product.	
7.1, Overall Study Design	This is a Phase 4, double-blind, randomized, placebo-controlled, multicenter study	This is a Phase **3b**/4, double-blind, randomized, placebo-controlled, multicenter study	Please refer to the previous explanation for this change.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
7.1, Overall Study Design	New language added.	**With the exception of liver transplant, if a subject experiences a suspected or confirmed clinical outcomes event, the subject should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for discontinuation outlined in the protocol. Subjects who discontinue investigational product are expected to be followed through to study closure (or at the discretion of the Sponsor). Additional information regarding subject follow-up and different options available to subjects is provided in Section 7.9 and Section 8.4.**	Please refer to the previous explanation for this change.
7.6, 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 7), investigational product should be initiated at a lower dose and subjects 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 7. Subjects ~~that~~ 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 terminate at the time when the needed number of	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 safety and/or** 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 7), investigational product should be initiated at a lower dose and subjects 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 7. 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 terminate at the time when the needed number of adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Table 7, and the Investigator assesses it as safe **to continue**. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. **If a subject discontinues investigational product and cannot continue to attend regularly scheduled study visits, the subject should be strongly encouraged to participate in study follow-up via phone calls or electronic medical record review as described in Section 7.9.**	Section was revised to reiterate the importance of collecting follow-up information for subjects who discontinue treatment and/or the study

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
	adjudicated events has accrued. If a subject reaches an outcome event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for mandatory interruption of investigational product outlined in Table 7, and the Investigator assesses it as safe. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination		
7.9, Subject Retention	A new section was created.	**The primary objectives for the end of study analysis are to evaluate the effects of OCA compared with placebo on all-cause mortality and liver-related clinical outcomes. The overall study duration is event driven and will be determined by the time required to observe the prespecified adjudicated events for the clinical outcomes' composite endpoint (Section 7.1). Therefore, it is critical that subjects continue to participate for the duration of the study to enable assessment of clinical outcomes and confirmation of the clinical benefit of OCA in PBC.** **Subjects may discontinue investigational product during the study; however, these subjects are expected to continue in the study until study termination and every effort will be made by the investigator to discuss subjects' continuation in the study. Even if a subject is no longer receiving investigational product, if the subject is attending study visits or participating in study follow-up, their information will contribute to the study primary endpoint and the evaluation of clinical benefit of OCA. All information collected in the study during regular study visits and through subjects participating in follow-up will contribute to the evaluation of safety of OCA and the scientific and medical understanding PBC.** **Investigators should emphasize to subjects the importance of their continuation in the study even after withdrawal of investigational product and discuss with subjects the various options for continued participation in the study:** • **Continuing to attend regularly scheduled visits, or**	A new section was created to provide guidance on the importance of retaining subjects in the study.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
		• **Allowing semi-annual telephone visits by the investigator, or** • **Allowing the investigator to have continued access to the subjects' medical records to assess suspected major adverse cardiovascular events (MACE) and liver-related clinical outcomes** **Subjects will be asked to provide both personal and primary physician(s) contact information who can provide information to the investigator about the clinical/medical status on the subjects' behalf.** **Should subjects choose to discontinue treatment or withdraw consent and fully leave the study, it will be made clear to them that they may return to their randomized treatment group should they so choose.** **Additional information is described in Section 8.4.** **Given the importance of subject retention, clinical site personnel should refer to specific strategies and procedures as described in a separate Subject Retention Plan that will provide additional information to facilitate subject retention.**	
8.2, Subject Inclusion Criteria	5. Contraception: Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below: • ~~Barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide~~ • Intrauterine device (IUD) • Vasectomy (partner) • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)	5. Contraception: Female subjects **must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥1 highly effective method of contraception** during the study and for 30 days **after the end of treatment**. **Highly effective methods of contraception per the CTFG guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of contraception are as follows:** • Intrauterine device - intrauterine device (IUD) - **intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • Vasectomy (partner) • **Combined (estrogen and progestogen containing) hormonal contraception (eg, oral, intravaginal or transdermal) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or**	Please refer to previous reason for this change.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
	Abstinence, if in line with the preferred and usual lifestyle of the subject	**female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.** • **Progestogen-only hormonal contraception (eg oral, injectable or implantable) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.** • **Sexual** abstinence, if in line with the preferred and usual lifestyle of the subject **(where abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).**	
8.3, Subject Exclusion Criteria	5.Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions ~~such as chronic lymphocytic leukemia~~)	5. Other medical conditions that may diminish life expectancy, including known cancers (except carcinomas in situ or other stable, relatively benign conditions)	Please refer to the previous reason for this change.
8.4, Subject Withdrawal Criteria	Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. See Section 7.6 for withdrawal criteria related to potential hepatic injury and/or decompensation including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.1 ~~below~~.	Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. See Section 7.6 for withdrawal criteria related to potential hepatic injury and/or decompensation including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.1**. The specific reason(s) for discontinuation from investigational product and/or withdrawal of consent should be recorded on the appropriate CRF.**	Revisions were made to underscore the importance of providing the specific reason(s) why a subject discontinued treatment and/or withdrew consent.
8.4.1, Other Reasons for	The following events are considered appropriate reasons for a subject to	**In general, the site should counsel the subject on the importance of maintaining the regular visit schedule and remaining on investigational**	Please refer to the earlier

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
Discontinuation of Study or Investigational Product	discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor): • Subject begins treatment with commercially available ~~OCA~~ • The Investigator or Sponsor considers that it is advisable or in the best interest of the subject. • 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 subject 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.	**product. Subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Subjects who discontinue investigational product prior to termination of the study need to also continue to follow the regular visit schedule through to study closure. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Specific strategies to encourage continued subject participation in the study will be outlined in a Subject Retention Plan. Subjects who discontinue investigational product but agree to follow up either through phone calls or review of electronic medical records are expected to continue to provide information regarding clinical outcomes or new interventions for PBC (such as initiating commercial OCALIVA). Early termination procedures should only be conducted if the subject withdraws consent (see Section 9.7.15).** The following events are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination (or at the discretion of the Sponsor): • Subject begins treatment with commercially available **OCALIVA.** - If a subject begins treatment with commercially available OCALIVA, they must interrupt IP immediately and this must be reported in the treatment discontinuation eCRF to prevent double dosing and for notification of the sponsor and medical monitor. • The Investigator or Sponsor considers that it is advisable or in the best interest of the subject. • 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 subject discontinues both investigational product and study visits and procedures).	response for the reason for change.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
	– Early termination procedures should be conducted if the subject withdraws consent (See Section 9.7.15). The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.	– Consent may be modified to discontinue study visits, but allow semi-annual telephone contact **of subject, subject's primary care physician, or personal contacts who can provide information on behalf of the subject by the investigator** – Consent may be modified to discontinue study visits or semi-annual telephone contact, but **may** allow **for** continued access to medical records to assess for suspected major adverse cardiovascular events (MACE), liver-related clinical outcomes, **and new interventions and medications for treatment of PBC.** – **Other subject follow-up options to collect study outcomes should be pursued according to local laws and regulations. If one of these alternate methods to collect study outcomes is acceptable to the subject, then the subject will be deemed not to have withdrawn consent for follow-up.** Early termination procedures should be conducted if the subject withdraws consent (see Section 9.7.15). The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.	
8.4.2, Withdrawal of Consent	If the subject 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 subjects 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 subject discontinuation. This information and date must be recorded in the appropriate case report form (CRF).	If the subject 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 subjects volunteer for the study and that they may withdraw their consent to continue in the study at any time. **Diligent efforts** must be made to determine the reason(s) for subject discontinuation **(such as initiation of commercial OCALIVA or underlying adverse events).** This information and date must be recorded in the appropriate case report form (CRF).	Revisions were made to provide guidance to Investigators on how to document the specific reasons why a subject withdrew consent.
8.4.3, Requirements to	New section added	**Subjects who wish to re-initiate investigational product while participating in study follow-up or re-enter the study after having withdrawn consent**	Revisions were made to

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
Re-Initiate Investigational Product or Re-Enter the Study		**more than 3 months since the last visit must confirm that they have not received any investigational product that is being evaluated for the treatment of PBC within 30 days or Commercial OCALIVA for three months before restarting investigational product or within 5 half-lives of the compound (whichever was longer). Subjects are to be re-consented and new baseline visit procedures must be performed.**	provide guidance to Investigators on study procedures for subjects who re-enter the study after having withdrawn consent.
8.4.3, Lost to Follow Up	If a subject fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the subject, he or she will be withdrawn from the study. ~~A reasonable effort must be made~~ to ~~contact the subject and~~ determine the reason(s) why a subject ~~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 CRF.	If a subject fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the subject, he or she will be withdrawn from the study. **Diligent efforts** to determine the reason(s) why a subject **failed** to return for a study visit or is lost to follow-up **must be made. If the subject has provided consent, the subject's primary care physician or personal contacts who can provide information on behalf of the subject by the investigator, must be contacted if the subject consistently fails to return for study visits.** This information and date of contact must be recorded in the appropriate CRF.	Revisions were made to provide options for follow up of subjects who discontinue.
8.4.4, Subject Discontinuation Notification	The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), ~~a reasonable effort~~ should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the	The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow up" (fails to return for a visit), **diligent efforts** should be made to contact the subject in order to determine why the subject failed to return **(see Section 8.4.3).** This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.15, Early Discontinuation and/or Early Termination Procedures).	Please refer to earlier reason for this change.

<table>
<tr><th>Section</th><th>Original Text (Amendment 5, 04 Jan 2018)</th><th>Revised Text (Version 6, 05 Nov 2019)</th><th>Justification for Change</th></tr>
<tr><td></td><td>EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (See Section 9.7.15, Early Discontinuation and/or Early Termination Procedures).</td><td></td><td></td></tr>
<tr><td>9.7.1, Visit Windows</td><td>New row for study re-entry was added.</td><td><table><tr><th>Visit or Procedure</th><th>Visit Window and/or Interval</th></tr><tr><td>IP Re-Initiation/ Study Re-Entry
(When a subject has previously discontinued treatment/ withdrawn consent and has chosen to return to study participation)</td><td>Day 0 procedures should be conducted and the visit window will be relative to Day 0 from the original study entry.</td></tr></table></td><td>Clarification of study procedures for subjects who re-enter the study.</td></tr>
<tr><td>9.7.15. Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent</td><td>Subjects ~~that~~ discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor.</td><td>Subjects who discontinue investigational product are expected to continue in the study until the end of the study, and the study will only terminate at the time when the needed number of adjudicated events has accrued or at the discretion of the Sponsor. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. Even if a subject is no longer receiving investigational product, if the subject is attending study visits or participating in study follow-up (through telephone visits or electronic medical record review), their information will contribute to the study primary endpoint and the evaluation of clinical benefit of OCA. All information collected in the study during regular study visits and through subjects participating in follow-up will contribute to the evaluation of safety of OCA and the scientific and medical understanding of PBC.</td><td>Please refer to earlier justification for this change.</td></tr>
<tr><td></td><td>A new footnote (footnote b) was to Table 8.</td><td>Table 8: Early Discontinuation Scenarios<table><tr><th></th><th>Investigational Product</th><th>Consent</th><th>Study Visit Status</th><th>EOT Visit[a]</th><th>EOS Visit[a]</th></tr><tr><td>Early Termination[b]</td><td>Discontinued</td><td>Withdrawn</td><td>No additional visits except EOT/EOS</td><td colspan="2">Combined Visit, Completed as close as possible to last dose IP</td></tr></table></td><td>Please refer to earlier justification for this change.</td></tr>
</table>

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change

Treatment Discontinuation[b,c]	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	Discontinued	Semiannual contact[d]	Telephone contact every 6 months (±2 weeks)	Combined Visit, Completed as close as possible to last dose IP	
	Discontinued	Record review only[d]	Record review only	Combined visit Completed as close as possible to last dose IP	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit Completed as close as possible to last dose IP	
Pregnancy	Interrupted	Retained	Regular Visit Schedule	Complete as close as possible to last dose IP	Complete at Final study visit
	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; IP = investigational product

[a] Refer to Section 7.1.1 Schedule of Study Procedures, Table 2 for all procedures and evaluations required at the End of Treatment and End of Study Visits.

[b] **Subjects may choose to re-consent, re-enter the study, and re-initiate IP at a later date. Day 0 procedures will be repeated and the subject will resume in the visit window relative to the original Day 0.**

[c] Includes initiation of commercially available OCA.

[d] Outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data. Additional data such as information on concurrent medical conditions, co-morbidities, relevant adverse events, and concomitant medications may be collected to help facilitate adjudication of these post-study events.

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
9.7.15, Early Discontinuation and/or Early Termination Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent	New language added.	During the EOT/EOS Visit: **For subjects who prematurely terminate investigational product and/or the study, procedures outlined in Section 8.4.1 should be followed.** **Subjects who wish to re-initiate investigational product while participating in study follow-up or re-enter the study after having withdrawn consent or having discontinued treatment more than 3 months since the last visit must confirm that they have not received any investigational product being evaluated for the treatment of PBC within 30 days or commercial OCALIVA for three months before restarting investigational product or within 5 half-lives of the compound (whichever was longer). Subjects are to be re-consented and new Day 0 visit procedures must be performed. The subject will resume the study in the visit window relative to their original Day 0 visit.**	Please refer to earlier justification for this change.
12.1.1.5, Suspected Unexpected Serious Adverse Reactions	New section was added.	**A suspected unexpected serious adverse reaction (SUSAR) is defined as a suspected adverse reaction which is assessed as serious, causally related to the investigational product, and unexpected per the reference safety information (RSI) in the Investigator's Brochure.** **SUSARs are subject to expedited reporting. The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening are recorded and reported as soon as possible to the relevant competent authorities (either directly or through the Eudravigilance Clinical Trials Module, as applicable), and to the Ethics Committees, no later than 7days after knowledge by the Sponsor of such a case. Relevant follow-up information is subsequently communicated within an additional 8 days. All other SUSARs shall be reported to the competent authorities concerned (either directly or through the Eudravigilance Clinical Trials Module) and to the Ethics Committees concerned, within a maximum of 15 days of first knowledge by the Sponsor. Each competent authority shall ensure that all SUSARs to an investigational product which are brought to its attention are recorded. The Sponsor shall also inform all participating Investigators, as applicable to the local regulations.**	Updated AE reporting requirements for SUSARs

Section	Original Text (Amendment 5, 04 Jan 2018)	Revised Text (Version 6, 05 Nov 2019)	Justification for Change
14.1, Study Monitoring	The Investigator may exercise judgment in allowing the CRA access to particular sections of the subject's medical records if these are deemed ~~irrelevant~~ to the performance, observations or conduct of this study.	The Investigator may exercise judgment in allowing the CRA access to particular sections of the subject's medical records if these are deemed **relevant** to the performance, observations or conduct of this study.	Revision was made to correct a typographical error
17.3, Regulatory Documentation	• Form FDA 1572	• Form FDA **1572 or equivalent form for the Investigator's region**	Revision was made for clarification purposes.

ADDENDUM 1 TO PROTOCOL 747-302

Netherlands-specific monitoring of subjects receiving CYP2D6 substrates with a narrow therapeutic index

PURPOSE

To implement additional monitoring by investigators for subjects in the Netherlands receiving CYP2D6 substrates with a narrow therapeutic index, such as tricyclic antidepressants (TCAs), concomitantly with investigational product (obeticholic acid; OCA).

OVERVIEW AND RATIONALE

The following guidance is being provided based on feedback from the Medical Ethics Review Committee overseeing the 747-302 study in the Netherlands. The Committee noted that specific data on drug interactions in subjects receiving CYP2D6 substrates with a narrow therapeutic index, such as TCAs, concomitantly with investigational product (OCA) are limited and recommended the implementation of additional monitoring in subjects who fall into this category.

Currently there is no evidence of clinically meaningful interactions between OCA and CYP2D6 substrates. The current United States Package Insert and European Union Summary of Product Characteristics for Ocaliva®, in Section 7 and Section 4.5, respectively, include potential interactions with warfarin, CYP1A2 substrates with a narrow therapeutic index, and bile acid binding resins but do not include specific mention of a potential interaction with CYP2D6 substrates with a narrow therapeutic index, consistent with the lack of evidence, at present, of clinically meaningful interactions between OCA and CYP2D6 substrates. However, as data are limited, the Sponsor has agreed to incorporate the requested additional monitoring for subjects in the Netherlands concomitantly receiving TCAs.

All information including, but not limited to, inclusion/exclusion criteria and study procedures provided in the current approved version of the study protocol should continue to be followed, in addition to the guidance provided below as a supplement to protocol Section 9.2 Concomitant Medications.

9.2 CONCOMITANT MEDICATIONS

9.2.2 Additional Guidance to the Investigator

Subjects that receive CYP2D6 substrates with a narrow therapeutic index, such as TCAs, concomitantly with investigational product will require additional oversight by the Investigator. Oversight should include close review of potential adverse events (AEs) associated with CYP2D6 substrates with a narrow therapeutic index and evaluation of untoward events including worsening of psychiatric symptoms. Dose adjustments to concomitant CYP2D6 substrate and/or investigational product should be made based

upon the Investigator's clinical judgement and on the safety, tolerability, and efficacy of the substrate.

The Sponsor will continue to evaluate and discuss Investigator concerns regarding AEs associated with the use or discontinuation of CYP2D6 substrates to ensure protection of subjects enrolled in the 747-302 study.

Appendix 1 Addendum Approval/Acceptance

Sponsor Signature

PPD

Interc _____ Date 1/18/17

PPD PhD
PPD Clinical Development
Intercept Pharmaceuticals, Inc.

Investigator's Signature:

I have received and read the current version of the Investigator's Brochure (IB) for INT-747 (OCA/Obeticholic acid) and this Protocol 747-302 Addendum 1. Having fully considered all the information available, I agree that it is ethically justifiable to give INT-747 to selected subjects/patients according to this protocol.

I understand that all information concerning INT-747 supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this trial and not previously published is confidential information. This includes the IB, Clinical Trial Protocol, CRFs, 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 747-302 and its addendum and in accordance with Good Clinical Practice (CPMP/ICH/135/95), 21CFR Part 312, and all applicable regulatory requirements.

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

_____ _____

Investigator Date

_____

Print Name

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Addendum 2: 27 April 2017

EudraCT Number: 2014-005012-42

Sponsor

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

TEL: 858-650-6398

SPONSOR'S APPROVAL OF THE PROTOCOL ADDENDUM

Reviewed and Approved by:

PPD

PPD PhD

PPD Clinical Development
Intercept Pharmaceuticals, Inc.

4/28/17

Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA), Protocol 747-302, 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 addendum.

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 (CRFs), 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 747-302 and this addendum, 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

PROCEDURES IN CASE OF EMERGENCY

Sponsor Contact Information

Medical Monitor – 24-hour Emergency Reporting

Primary Contact:	PPD MD, Medical Director, Drug Safety, Intercept Pharmaceuticals, Inc.
Mobile:	PPD
Telephone:	PPD (Pacific time zone)
Email:	PPD
SAE Fax:	+1 800 497 8521
SAE Email:	sae@interceptpharma.com

Or if Not Available:

Contact:	PPD MD, PhD, Medical Director, Clinical Research, Intercept Pharmaceuticals, Inc.
Mobile:	PPD
Telephone:	PPD (Pacific time zone)
Email:	PPD

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
AE	adverse event
APRI	aspartate aminotransferase to platelet ratio index
CRF	case report form
ELF	enhanced liver fibrosis
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
IB	Investigator's Brochure
OCA	obeticholic acid
PBC	primary biliary cholangitis (also known as primary biliary cirrhosis)
TE	transient elastography

4. OVERVIEW AND RATIONALE

Study 747-302 is a Phase 4[1], double-blind, placebo-controlled, multicenter study to investigate the effects of obeticholic acid (OCA) in subjects with primary biliary cholangitis (PBC, also called primary biliary cirrhosis), with high risk of liver-related clinical complications.

Liver biopsy is no longer mandatory for diagnosis of PBC; however, biopsies can provide important information to assess the severity of the disease, as well as prognosis, progression, and response to treatment. A paired biopsy substudy was, therefore, recommended by Regulatory Authorities, to further assess clinical outcomes in terms of histological progression to cirrhosis. This addendum[2] to the 747-302 Study Protocol defines the paired biopsy substudy to assess the effect of OCA versus placebo on the histological severity of disease (fibrosis/cirrhosis) in subjects with PBC. This substudy will also explore the relationship between histological changes in the liver versus clinical, laboratory, and noninvasive measures indicative of progression to cirrhosis in subjects with PBC treated with OCA.

All information including, but not limited to, inclusion/exclusion criteria and study procedures provided in the current approved version of the study protocol should be followed, in addition to the guidance provided below.

5. OBJECTIVES

Primary Objective

- To assess the effect of OCA compared to placebo on the histological severity of PBC by assessing the following:
  - Progression to cirrhosis, in subjects who are noncirrhotic at Baseline
  - Improvement in fibrosis/cirrhosis, in subjects who are cirrhotic at Baseline

Secondary Objectives

- To assess the effect of OCA on the histological changes in the liver
- To assess the relationship between histological changes and measurements (clinical, laboratory, and noninvasive) indicative of progression to cirrhosis in subjects with PBC. Noninvasive measurements include the following:
  - Transient Elastography (TE)
  - Noninvasive scores of liver fibrosis including enhanced liver fibrosis (ELF), and aspartate aminotransferase to platelet ratio index (APRI)

[1] Study 747-302 is considered a Phase 4 study in regions where OCA has received regulatory approval for primary biliary cholangitis (PBC, also called primary biliary cirrhosis), ie, in the US and the EU; in all other regions, this study is considered Phase 3b. In May 2016, the United States Food and Drug Administration (FDA) granted accelerated approval for OCA (Ocaliva) for the treatment of PBC. In December 2016, Ocaliva received Conditional Approval from the European Medicines Agency's Committee for Medicinal Products for Human Use.
[2] Note: Addendum 1 (dated 18 Jan 2017) to protocol 747-302 is a country-specific addendum.

6. DETAILS OF THE ADDIONAL PROCEDURES

SUBJECT POPULATION AND STUDY CENTERS

Number of Subjects: This substudy will enroll approximately 45 subjects.

Eligibility:

- Subjects who are participating in the 747-302 study and meet all eligibility criteria in the current version of the main protocol.
  - For subjects who require a baseline biopsy, Screening Visit 1 data should be available, and a preliminary eligibility assessment should be performed, before the baseline biopsy sample is collected.
  - Subjects must remain enrolled in the main protocol to continue participation in biopsy substudy.
- Must provide written informed consent and agree to comply with the requirements of the substudy protocol.
- Is able to safely undergo a liver biopsy, in the opinion of the Investigator.
- Subjects currently enrolled in the study who have not yet presented with signs and symptoms of progression to cirrhosis may also participate, provided a biopsy sample obtained ≤6 months prior to Day 0 is available.

Study Centers: All sites participating in the 747-302 study with the capability to perform serial biopsies may participate in this optional substudy.

STUDY PROCEDURES

In addition to the procedures described in Section 7.1 of the main study protocol, the subjects enrolled in the biopsy substudy will also complete biopsy and additional noninvasive fibrosis assessments described in this addendum.

Biopsy

The goal of this substudy is to maximize the availability of data while minimizing the number of biopsies performed. Thus, all subjects who consent to participate in this substudy will undergo a biopsy at Baseline (if none available from ≤6 months prior to Day 0) prior to initiating investigational product, and, based on the results of that biopsy, again upon clinical evidence of progression to cirrhosis or at the end of the treatment (EOT) or End of Study (EOS); see Table 1). This strategy will allow for both histological confirmation of progression to cirrhosis, as well as possible histological improvement following treatment with OCA.

Table 1: Timing of Second Biopsy

If Baseline biopsy result is:	*then second biopsy will be obtained at:*
Noncirrhotic	• The time of presentation of clinical signs and symptoms of cirrhosis, or • The EOT (if the subject will continue to attend study visits) or EOS visit if no presentation of clinical signs and symptoms of cirrhosis during study, whichever comes first
Cirrhotic	• EOT (if the subject will continue to attend study visits) or EOS, whichever comes first

EOT = end of treatment; EOS = end of study

Biopsy-Related Assessments:

- **Baseline Biopsy** may be performed at any time after the Screening Visit 1 eligibility criteria have been reviewed and prior to Day 0. If a biopsy was obtained no more than 6 months before Day 0 and slides or sample quantity are sufficient and suitable for baseline reading, a biopsy at Screening need not be repeated. Baseline biopsy must be collected prior to the first dose of the investigational product.
- **Post-treatment Biopsy**: If a subject develops evidence of probable progression to cirrhosis as assessed by the indicators listed below, the post-treatment biopsy will be performed as close as possible to when progression to cirrhosis is determined by the Investigator, and within approximately 3 months of progression. Biopsy reports and available clinical, laboratory, and radiological assessments will be used as a basis for adjudication by the hepatic outcomes adjudication committee to assure that all events of progression to cirrhosis meet predefined criteria and are consistent across sites.
- **EOT or EOS Biopsy**: Biopsy will be performed as part of the EOT/EOS procedures on all subjects who have not already had a post-treatment biopsy based on evidence of the clinical, laboratory, or radiological indicators of progression to cirrhosis during the course of the study. If, for scheduling purposes, a biopsy cannot be completed as part of the EOT/EOS Visit, the biopsy should be scheduled as close as possible to the actual EOT/EOS Visit date.

Non-invasive Fibrosis Assessments:

TE will be performed when a subject develops evidence of probable progression to cirrhosis. In addition, laboratory samples needed to obtain noninvasive scores of liver fibrosis (ELF and APRI) will also be collected at the time a subject develops evidence of probable progression to cirrhosis.

ASSESSMENT OF EFFICACY

Liver Biopsy Instructions and Central Reading of Liver Histology

Full instructions concerning the number and type of samples to be collected at each visit, the sample collection methods, sample processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. Collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

Liver biopsies will generally be obtained from the right lobe of the liver as described in a study-specific histology manual. If the initial biopsy was obtained from the left lobe, then subsequent biopsies should be obtained from the left lobe, and vice versa.

All biopsy assessments, including screening and histology efficacy assessments, will be performed by study pathologist/central reader blinded to the treatment group assignment. The biopsies will be graded by a central reader using a pre-defined scoring system. Detailed information related to biopsy scoring will be provided to the central reader by the Sponsor in a study-specific histology manual.

Paired biopsies (Screening/Baseline biopsy and post-treatment [or EOT/EOS] biopsy) will be read by a central reader blinded to the treatment group assignment.

Biopsy Criteria for Progression to Cirrhosis

The following criteria will be used for adjudication of progression to cirrhosis:

- Persistent (ie, 2 consecutive measurements obtained at least 3 months apart) elevation in Fibroscan® TE >16.9 kPa, AND/OR
- Presence of any of the following:
  - 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 any of the following criteria:
    - Persistent decrease in serum albumin, OR
    - Elevation in prothrombin time/international normalized ratio (not due to antithrombotic agent use), OR
    - Elevated total bilirubin >2x upper limit of normal

Transient Elastography

TE assessment will be performed at the investigational sites, where the device is available, using the Fibroscan instrument (Echosens, Paris, France), to assess liver fibrosis.

Noninvasive Scores of Liver Fibrosis

ELF score will be calculated using an algorithm that combines serum values of tissue inhibitor of metalloproteinases-1, procollagen type-3 N-terminal propeptide, and hyaluronic acid. Likewise, APRI score will be obtained from serum aspartate aminotransferase and platelet values.

ASSESSMENT OF SAFETY

Safety assessments will be performed as in Section 12 of the main protocol. In addition, the Investigator will document her/his opinion of the relationship of the adverse events (AEs) to liver biopsy using the criteria outlined in Table 2.

Table 2: Relationship of Adverse Events to Liver Biopsy

Relationship	Description
Related	A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.
Not Related	Any event that does not meet the above criteria.

STATISTICAL METHODS

Primary Efficacy Analysis

For each treatment group, the number and the proportion of subjects with and without biopsy-assessed cirrhosis determined at EOT/EOS will be presented in a shift table from Baseline to the EOT/EOS, separated for two baseline biopsy-assessed cirrhosis status (ie, cirrhosis versus noncirrhosis). For baseline noncirrhotic subjects without an EOT/EOS biopsy, the cirrhosis status will be presented in a shift table from Baseline to the time when a post-treatment biopsy is performed. The proportion of subjects that have cirrhosis status change will be compared between OCA treatment group and placebo group.

In addition, for the subset of subjects who were noncirrhotic at Baseline, Kaplan-Meier estimates of the time to cirrhosis (as assessed by biopsy) will be summarized and graphed by treatment group.

Secondary Efficacy Analyses

The TE, ELF and APRI scores will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The change from Baseline and percentage change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations before treatment. Further details will be specified in the statistical analysis plan.

Determination of Sample Size

Based on the participation of approximately 10% of subjects in the optional biopsy component of the Phase 3 Study 747-301[3], a similar percent of subjects are expected to consent to participate in this substudy. With total enrollment anticipated to be 428 subjects, approximately 45 subjects are expected to enroll in this substudy.

Assuming 45 subjects are noncirrhotic at Baseline, the biopsy data from 45 subjects will provide 73% power to detect a difference in the event rate of progression to cirrhosis when OCA event rate is 0.23 (approximately 50% risk reduction); or 59% power to detect a difference in the event rates of progression to cirrhosis when OCA event rate is 0.28 (approximately 45% risk reduction) at a significance level of 0.1 for a one-sided test and placebo group's event rate is 0.5. The above statistical justification is based on the assumptions that the biopsy substudy will have subjects with a close to 1:1 ratio between placebo and OCA arm.

[3] A Phase 3, Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis. ClinicalTrials.gov number, NCT01473524.

ADJUDICATION COMMITTEE

Adjudication of progression of cirrhosis will be performed by an independent hepatic outcomes adjudication committee (refer to Section 13.4 in "Adjudication Committee" subsection of the main protocol). All available documentation of progression to cirrhosis, including biopsy reports, will be made available to the adjudicators.

Clinical Study Protocol 747-302

OBETICHOLIC ACID (OCA)

A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

THE COBALT STUDY

Clinical Outcomes with OBeticholic Acid in Liver Treatment (COBALT)

Addendum 1: 02 Jan 2018

Country-Specific Addendum for Turkey

EudraCT Number: 2014-005012-42

Sponsor

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4760 Eastgate Mall
San Diego, CA 92121

USA

TEL: 858-652-6800

FAX: 858-558-5961

SPONSOR'S APPROVAL OF THE PROTOCOL ADDENDUM

Reviewed and Approved by:

PPD

PPD PhD

PPD Clinical Development

Intercept Pharmaceuticals, Inc.

8 JAN 2018

Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA), Protocol 747-302, 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 747-302 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 747-302: TURKEY

1. OVERVIEW AND RATIONALE

The purpose of this Country-Specific Protocol Addendum (dated 02 Jan 2018) is to revise the study phase from Phase 4 to Phase 3b in Turkey for Protocol 747-302. Obeticholic acid (OCA) has received regulatory approval in a number of regions (United States, European Union, and Canada) for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Based on this regulatory approval, the phase of the 747-302 study changed to Phase 4 with Protocol Version 4 to reflect that this study is now considered a post-marketing study in these regions, where the majority of participating sites and countries in the 747-302 study are also located. However, as OCA has not yet received regulatory approval in Turkey, this addendum was issued to document that Study 747-302 is considered a Phase 3b study in Turkey.

The following referenced sections of the protocol reflect this change:

Title Page and Synopsis, Title of Study: A Phase 3b, Double Blind, Randomized, Placebo Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Subjects with Primary Biliary Cholangitis

Synopsis, Phase of Development: 3b

Synopsis, Methodology:
This Phase 3b, double-blind, randomized, placebo-controlled, multicenter study will evaluate the effect of OCA on clinical outcomes in subjects with PBC.

Section 7.1, Overall Study Design

This is a Phase 3b, double-blind, randomized, placebo-controlled, multicenter study.

A copy of this addendum should be filed alongside the current approved version of the study protocol at all investigative sites in Turkey. All information including, but not limited to, inclusion/exclusion criteria and study procedures provided in the current approved version of the study protocol should continue to be followed.