Clinical Trial Protocol 747-207

OBETICHOLIC ACID

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding, Clinical Trial Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects with Primary Sclerosing Cholangitis

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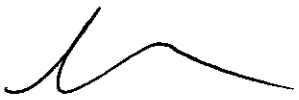
SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:



18 MAR 2016

Leigh MacConell, PhD

Vice President, Clinical Development
Intercept Pharmaceuticals, Inc.

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 747-207. 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 trial and not previously published is confidential information. This includes the IB, Clinical Trial Protocol, Case Report Forms (CRF) and any other nonclinical 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 747-207 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 trial has the right to discontinue the trial at any time.

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

PROCEDURES IN CASE OF EMERGENCY

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1. 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)

Title of Trial: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding, Clinical Trial Evaluating the Efficacy and Safety of Obeticholic Acid in Subjects with Primary Sclerosing Cholangitis

Trial Number: 747-207

Number of Subjects: Approximately 75

Planned Number of Trial Sites: Approximately 35 (Europe and United States [US])

Trial Period (Months): Approximately 50 months **(**first subject consented to last subject completing last study visit)

Phase of Trial: Phase 2

Objectives:

Primary

To evaluate the effects of OCA on the following in subjects with primary sclerosing cholangitis (PSC):

- Serum alkaline phosphatase (ALP)
- Safety

Secondary

To evaluate the effects of OCA on the following in subjects with PSC:

- Hepatic biochemistry and indices of function
- Markers of:
  - Hepatic fibrosis and GI inflammation and disease
  - Farnesoid X receptor (FXR) activity
  - Inflammatory bowel disease (IBD)
- Pharmacokinetics (PK) of OCA and other bile acids
- Exposure response of total OCA (OCA and its conjugates) to biomarkers (eg, ALP and bile acids)
- Long-term efficacy and safety of OCA
- Disease-specific symptoms.

Methodology:

Double-blind Phase (DB)

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-finding evaluation of the efficacy and safety of OCA in subjects with PSC. Approximately 75 subjects who provide written informed consent and meet all of the inclusion and none of the exclusion criteria will be randomized to 1 of 3 treatment groups as follows: 1.5 mg titrating to 3 mg OCA, 5 mg titrating to 10 mg OCA, or placebo, in a 1:1:1 ratio. Subjects will administer investigational product orally, once daily for 2 consecutive 12-week periods.

For the first 12 weeks, the subject's dose will be 1.5 mg OCA, 5 mg OCA, or placebo. After 12 weeks, the subject's dose will be titrated as follows, providing there are no limiting safety or tolerability concerns in the opinion of the Investigator, while maintaining the trial blind: the 1.5 mg OCA treatment group will titrate to 3 mg, the 5 mg OCA treatment group will titrate to 10 mg OCA, and the placebo group will remain on placebo. DB treatment will continue for a further 12 weeks at that dose.

Any subjects whose dose is not titrated, due to safety or tolerability concerns, will remain on their starting treatment (1.5 mg OCA, 5 mg OCA, or placebo) for the remainder of the DB phase to Week 24.

Randomization will be stratified by the presence or absence of concomitant ursodeoxycholic acid (UDCA) use and total bilirubin level (≤1.5x upper limit of normal [ULN] or >1.5x ULN but <2.5x ULN).

Long-Term Safety Extension Phase (LTSE)

Following completion of participation in the DB phase, subjects will be asked to reconfirm their consent for participation in the open-label long-term safety extension (LTSE) phase (a further 24 months).

Upon a subject's completion of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA unless safety and tolerability warrant a dose reduction to 5 mg.

- Placebo at end of DB → 5 mg OCA in LTSE
- 3 mg OCA at end of DB → 5 mg OCA in LTSE
- 10 mg OCA at end of DB → 10 mg OCA in LTSE

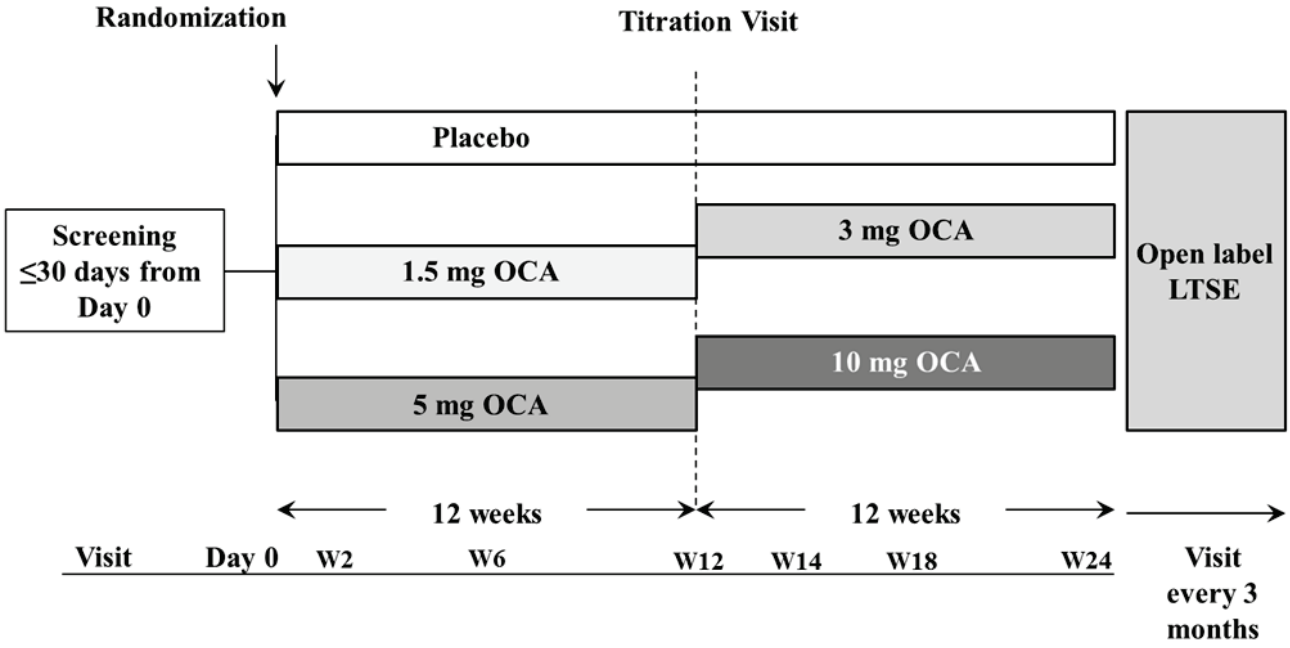
Those subjects who did not up-titrate their dose at Week 12 in the DB phase can remain on their DB dose, or commence at 5 mg at the decision of the Investigator based on safety and tolerability of the DB dose at Week 24. If an investigator does not wish for a subject to be titrated in line with the above schedules, this may be discussed with the Medical Monitor.

During the LTSE phase, subjects may titrate to higher doses of OCA, at a frequency not greater than 3 monthly (ie, at each of the scheduled LTSE visits), up to a maximum dose of 10 mg daily. The guideline for an increase in the dose of OCA is based on tolerability and the goal of achieving an ALP level <1.5x ULN. Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg. Intermediate doses

(eg, 6.5 mg) may be considered as deemed appropriate by the Investigator. Dose should not exceed 10 mg.

The Investigator may decrease the dose of OCA, or dosing frequency, in line with safety and tolerability as required for that subject. Following a change in OCA dose or dose frequency, an Investigator may be permitted to return the subject to a prior dose or dosing frequency and this should be discussed with the Intercept Medical Monitor in advance.

Trial Design Schematic



Diagnosis and Main Criteria for Inclusion:

Subjects must meet all of the following to be eligible to participate:

1. Male or female aged 18 to 75 years
2. Must provide written informed consent and agree to comply with the trial protocol
3. Must have a diagnosis of PSC (based on cholangiography at any point in time)
4. ALP at Screening ≥2x ULN
5. Total bilirubin at Screening <2.5x ULN.

   Note 1: Subjects will be stratified according to total bilirubin level and no more than 25% of subjects recruited will have a total bilirubin >1.5x ULN and <2.5x ULN at Screening.
6. For subjects with concomitant IBD:
   a. Colonoscopy (if the subject has a colon) or other appropriate endoscopic procedure within 12 months of Day 0 confirming no dysplasia or colorectal cancer
   b. Subjects with Crohn's Disease (CD) must be in remission as defined by a Crohn's Disease Activity Index (CDAI) <150.

c. Subjects with ulcerative colitis (UC) must either be in remission or have mild disease. Remission is defined as a partial Mayo score of ≤2 with no individual sub-score exceeding 1. Mild disease is defined as a partial Mayo score ≤3 with no individual sub-score exceeding 1 point.

7. For subjects being administered UDCA as part of their standard of care, the dose must have been stable for ≥3 months prior to, and including, Day 0 and must not have exceeded 20 mg/kg/day during this time.

   Note 2: Subjects not taking UDCA at Day 0 must not have taken UDCA for ≥3 months prior to, and including, Day 0 and must not take UDCA during the DB period. Subjects will be stratified according to UDCA use, and no more than 50% of subjects administering UDCA at Day 0 will be enrolled.

8. Subjects being administered biologic treatments (eg, anti-TNF or anti-integrin monoclonal antibodies), immunosuppressants, systemic corticosteroids, or statins, must have been on a stable dose for ≥3 months prior to, and including, Day 0 and should plan to remain on a stable dose throughout the trial.

9. Contraception: female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the trial and until 4 weeks following the last dose of investigational product (including LTSE doses). Effective methods of contraception are considered to be those listed below:

   - Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm with spermicide; or
   - Intrauterine device; or
   - Vasectomy (partner), or
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
   - Abstinence, if in line with the preferred and usual lifestyle of the subject [where abstinence is defined as refraining from heterosexual intercourse during the trial duration (from first administration of investigational product until 4 weeks after the last dose of investigational product)]

Exclusion Criteria

Subjects will be excluded from trial participation if they meet any of the following:

1. Evidence of a secondary cause of sclerosing cholangitis at Screening
2. Immunoglobulin G4 (IgG4) >4x ULN at Screening or evidence of IgG4 sclerosing cholangitis
3. Small duct cholangitis in the absence of large duct disease
4. Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including:
   - Current Child-Pugh classification B or C

- History of, or current diagnosis or suspicion of, cholangiocarcinoma or other hepatobiliary malignancy, or biliary tract dysplasia
- History of liver transplantation, or current model of end stage liver disease (MELD) score ≥12
- History of, or current, cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma or hepatic encephalopathy (as assessed by the Investigator)
- Current known portal hypertension with complications, including known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds, or related therapeutic or prophylactic interventions (eg, beta blockers, insertion of variceal bands, or transjugular intrahepatic portosystemic shunt [TIPS])
- History of, or current, hepatorenal syndrome (type I or II) or Screening serum creatinine >2 mg/dL (178 μmol/L)
- Platelet count <50 $x10^9$/L

5. Current clinical evidence of dominant strictures that are considered clinically relevant in the opinion of the Investigator or current biliary stent at Screening
6. Current cholecystitis or evidence of current biliary obstruction due to gallstones. Asymptomatic gallstones that are not considered a safety risk in the opinion of the Investigator might be acceptable subject to discussion and agreement with the Medical Monitor
7. Colonic dysplasia within ≤5 years prior to Day 0
8. History of small bowel resection
9. History of other chronic liver diseases, including, but not limited to, primary biliary cirrhosis (PBC), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA), hepatitis C virus, and overlap syndrome
10. Known Gilbert's syndrome or history of elevations in unconjugated (indirect) bilirubin >ULN or unconjugated (indirect) bilirubin >ULN at Screening.
11. Known history of human immunodeficiency virus (HIV) infection
12. Currently experiencing, or experienced within ≤3 months of Screening, pruritus requiring systemic or enteral treatment.
13. Known or suspected acute cholangitis in the 3 months prior to, and including, Day 0 including cholangitis treated with antibiotics.
14. Administration of antibiotics is prohibited ≤1 month of Day 0 (unless subject is on a stable prophylaxis dose for at least 3 months prior to Day 0).
15. Administration of the following medications is prohibited ≤6 months of Day 0 and throughout the trial: fenofibrate or other fibrates and potentially hepatotoxic medications (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin).

16. IBD flare during Screening (up to and including Day 0), where "flare" is defined as follows:
    - UC flare: partial Mayo Score ≥5, and
    - CD flare: CDAI ≥250
17. Evidence of deleterious effects of alcohol abuse (as assessed by the Investigator) or excessive alcohol consumption (>4 units/day for males, >2 units/day for females)
18. Known or suspected use of illicit drugs or drugs of abuse (allowed if medically prescribed or indicated) within 3 months of Day 0
19. If female: known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
20. Other concomitant disease, malignancy, or condition likely to significantly decrease life expectancy to less than the duration of the trial (eg, moderate to severe congestive heart failure)
21. Participation in another investigational drug, biologic, or medical device trial within 30 days prior to Screening
22. History of noncompliance with medical regimens, or subjects who are considered to be potentially unreliable
23. Blood or plasma donation within 30 days prior to Day 0
24. Mental instability or incompetence such that the validity of informed consent or compliance with the trial is uncertain.

Investigational Product, Dosage and Mode of Administration: OCA, 1.5 mg tablet and matching placebo and OCA 5 mg tablet and matching placebo.

Doses will be 1.5 mg, 3mg, 5mg, 10 mg OCA or matching placebos, as follows:

DB phase: 2 tablets administered once daily during weeks 0 through 12 and 4 tablets administered once daily during weeks 12 through 24

LTSE Phase: All subjects will receive open-label OCA at a starting dose that is dependent upon their dose at completion of DB phase, as well as safety and tolerability. Doses may be 1.5 mg, 3 mg, 5 mg, or 10 mg, ie, 1 or 2 tablets, once daily. Intermediate doses (eg, 6.5 mg) may be considered as deemed appropriate by the Investigator. Dose should not exceed 10 mg.

Duration of Treatment: 30 months (6 month DB period followed by a 24 month, open-label LTSE)

Duration of Subject Participation: up to 32 months (up to 30 day Screening period, 6 month DB period, followed by a 24 month open-label LTSE period, and a 1 month follow-up period)

Criteria for Evaluation:

Primary Objectives	Assessments
Serum ALP	ALP
Safety	Adverse events (AEs) Clinical findings and laboratory values
Secondary Objectives	
Hepatic biochemistry and indices of function	ALP Albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR)
Markers of hepatic and GI inflammation, disease, and fibrosis	Autotaxin and its metabolites, calprotectin, C-reactive protein (CRP), Cytokeratin-18 (CK-18), Enhanced liver fibrosis (ELF) markers, Immunoglobulin A (IgA), IgG, Immunoglobulin M (IgM), Interleukin-6 (IL-6), Interleukin-12 (IL-12), Interleukin-23 (IL-23), Transient elastography (TE; at participating sites), Transforming growth factor-beta (TGF-β), Tumor necrosis factor-alpha (TNF-α)
Markers of farnesoid X receptor (FXR) activity	Fibroblast growth factor-19 (FGF-19)
PK of OCA and other bile acids	Plasma OCA bile acids and conjugates including 7α-hydroxy-4-cholesten-3-one (C4)
Exposure response of total OCA to biomarkers	Relationship of total OCA (OCA and its conjugates) to biomarkers such as change in ALP and change in bile acids.
Long-term efficacy and safety	As above
Disease-specific symptoms	Pruritus Visual Analogue Scale (VAS) Pruritus 5-D questionnaire Partial Mayo scoring system for assessment of ulcerative colitis activity (partial Mayo score) Crohn's disease activity index (CDAI)

Statistical Methods:

Efficacy Analyses

The primary efficacy endpoint is the Week 24 change from Baseline in ALP. The primary efficacy analysis will compare the Week 24 change from Baseline in ALP between the OCA 10 mg treatment group and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata, and Baseline as a covariate.

Secondary efficacy analyses of hepatic biochemistry and function parameters will use the same ANCOVA models as the primary endpoints. A hierarchical approach will be used for multiplicity adjustments. If the primary efficacy analysis is statistically significant ($p < 0.05$), the

following order will be used in the testing procedure to compare the change from Baseline in ALP between OCA and placebo:

- Week 12: OCA 5 mg treatment group (randomized to 5 mg for the initial 12 weeks followed by 10 mg for the latter 12 weeks) vs. placebo
- Week 24: OCA 3 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo
- Week 12: OCA 1.5 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo

If at any step the comparison is not statistically significant, then all subsequent comparisons will be exploratory rather than confirmatory.

In addition, secondary efficacy analyses of ALP response rates, defined as ALP to <1.5x ULN, will compare OCA treatment groups vs. placebo at Week 12 and Week 24 using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factor. Missing values will be considered a non-response.

Safety Analyses

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

Laboratory parameters and vital signs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized. Electrocardiograms (ECGs) will be summarized by treatment group using frequency at each visit. The shift from baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment (except for lipoprotein assessments where Baseline will be Day 0).

Pharmacokinetic and Pharmacodynamic Analyses

The pharmacokinetics (PK) of OCA and other bile acids will be evaluated, including AUC_t, C_{max}, and t_{max}. An exposure response analysis of total plasma OCA (OCA and its conjugates) to biomarkers, such as change in ALP and change in bile acids, will be performed to help identify optimal doses for this patient population.

Full details of the statistical methodology, analyses, and outputs will be detailed in the statistical analysis plan (SAP).

Interim Analysis

An unblinded interim analysis for planning purposes will be conducted after approximately 50% of subjects have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint: the change from Baseline in ALP, between OCA treatment groups (1.5 mg and 5 mg) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. No adjustments to the alpha level will be made.

Sample Size Justification

A sample size of 25 subjects per treatment group, a total of 75 subjects, will provide at least 90% power to detect a treatment difference for change in ALP assuming the mean absolute change in ALP for OCA and placebo treatment groups are approximately -20% and -5%, respectively, with a pooled standard deviation of 16, based on a 2-sided independent 2-group t-test at an alpha level of 0.05.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
AASLD	American Association for the Study of Liver Diseases
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC_t	area under the concentration time curve
β- hCG	beta human chorionic gonadotrophin
BAS	Bile acid sequestrants
BP	blood pressure
BUN	blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
CCA	cholangiocarcinoma
CCl_4	carbon tetrachloride
CD	Crohn's disease
CDAI	Crohn's disease activity index
CDCA	chenodeoxycholic acid
CFR	Code of Federal Regulations
CK-18	cytokeratin 18
C_{max}	maximum concentration observed
CRA	Clinical Research Associate
CRF	case report form
CRP	C-reactive protein
C_{ss}	steady state concentration
CYP7A1	cholesterol 7-α hydroxylase;
DB	double-blind
D/d	day/days
dL	deciliter
DSMC	Data Safety Monitoring Committee

Abbreviation or Specialist Term	Explanation
EASL	European Association for the Study of Liver
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
EOT	end of treatment
ERCP	endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FU	follow-up
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
Glyco-OCA	glyco-obeticholic acid
GMP	good manufacturing practice
HA	hyaluronic acid
HDL	high density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HR	heart rate
HSC	hepatic stellate cells
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG4	Immunoglobulin G4
IgM	Immunoglobulin M
IL	interleukin

Abbreviation or Specialist Term	Explanation
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
L	liter
LCA	lithocholic acid
LDL	low density lipoprotein
LTSE	long-term safety extension
MedDRA	medical dictionary of regulatory activities
MELD	model of end stage liver disease
µmol/L	micromoles per liter
mg	milligram
mRNA	messenger ribonucleic acid
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NMR	nuclear magnetic resonance
OCA	obeticholic acid
P3NP	procollagen-3 N-terminal peptide
PBC	primary biliary cirrhosis
PD	pharmacodynamic
PIS	patient information sheet
PK	pharmacokinetic
PSC	primary sclerosing cholangitis
RBC	red blood cell
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SUSAR	suspected unexpected serious adverse reaction
TAA	thioacetamide

Abbreviation or Specialist Term	Explanation
Tauro-OCA	tauro-obeticholic acid
TE	transient elastography
TEAE	treatment emergent adverse event
TG	triglycerides
TGF-β1	transforming growth factor – beta 1
TIMP-1	tissue inhibitor of metalloproteinase 1
TIPS	transjugular intrahepatic portosystemic shunt
t_{max}	time to C_{max}
TNF-α	tumor necrosis factor - alpha
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
U/L	units per liter
ULN	upper limit of normal
VAS	visual analogue scale
VLDL	very low density lipoprotein
W/wk	week
WBC	white blood cell

4. INTRODUCTION

4.1. Overview of Primary Sclerosing Cholangitis and Obeticholic Acid

Primary sclerosing cholangitis (PSC) is a rare, life-threatening, chronic cholestatic liver disease characterized by progressive destruction of bile ducts with eventual onset of cirrhosis and its complications. Despite evaluation of multiple treatments, liver transplant is currently the only treatment shown to improve clinical outcome.

PSC is usually diagnosed by preliminary assessment of liver biochemistry, with or without reported symptoms, and confirmed by cholangiography, typically magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography (ERCP). Alkaline phosphatase (ALP) is elevated in most PSC patients, consistent with cholestasis; alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) are typically elevated as well, but not in all cases. Bilirubin is often normal in early stage PSC but increases with progression of the disease. The mean age at diagnosis is 40 years, and men are affected twice as often as women.

PSC is a serious and life-threatening condition. Median survival for PSC patients has been previously estimated as 8 to 12 years from diagnosis in symptomatic patients, depending upon stage of the disease at the time of diagnosis (Levy 2006, Worthington 2006, Lee 1995). Complications involving the biliary tree are common and include cholangitis as well as ductal strictures and gallstones, both of which may require frequent endoscopic or surgical interventions. PSC is often complicated by the development of malignancies, with cholangiocarcinoma (CCA) being the most common. CCA drastically worsens mortality (Fevery 2007, Lazaridis 2006). In a large Swedish trial, the 5-year survival rate for patients diagnosed with either CCA or gallbladder cancer was approximately 5% compared to >85% survival in PSC patients without hepatobiliary cancer (Bergquist 2002).

Obeticholic acid (OCA) is a modified bile acid and is a potent agonist of the farnesoid X receptor (FXR). OCA has marked anti-fibrotic and anti-inflammatory properties in animal models of liver disease. In addition, the safety and tolerability of OCA has been evaluated in clinical trials in the 'sister' cholestatic liver disease, primary biliary cirrhosis (PBC). Phase 2 and Phase 3 trials in PBC subjects have shown that treatment with OCA resulted in highly statistically significant improvements in liver biochemistry associated with cholestasis and was generally well tolerated. These findings render OCA potentially useful for the treatment of PSC. OCA has received orphan drug designation for the treatment of PSC in Europe and the USA.

4.2. Mechanism of Action of Obeticholic Acid

For a detailed description of OCA's mechanism of action please refer to the current OCA Investigator's Brochure (IB). FXR is an essential and pleiotropic regulator of a variety of activities involved in bile acid homeostasis (Lefebvre 2009). Its activation affects genes that control bile salt synthesis and transport (Makishima 1999, Wang 1999); activation of FXR reduces the expression of messenger ribonucleic acid (mRNA) for cholesterol 7-α hydroxylase (CYP7A1; the rate-limiting enzyme of bile salt synthesis) and the sinusoidal bile salt uptake pump, while inducing the bile salt export pump. Activation of FXR in the ileum leads to increased release of fibroblast growth factor 19 (FGF-19) into the portal vein, transporting it to

the liver where it also acts as a brake on endogenous bile acid production by repressing CYP7A1 (Cipriani 2011, Pols 2011). In addition to being the key regulatory gatekeeper for bile acid synthesis, FXR has also been implicated as having a role in modulating immune response, decreasing portal hypertension, and potentially being anti-atherogenic (Lefebvre 2009).

Chenodeoxycholic acid (CDCA) is the principal natural ligand of FXR in humans. When cellular levels are already high, the negative feedback pathway inhibits the further synthesis of bile. CDCA, and its epimer ursodeoxycholic acid (UDCA), have a long history of use in of the dissolution of cholesterol gallstones (although currently laparoscopic surgery is more typically used). In cholestasis, the primary mode of action of UDCA is thought to be choleretic, ie, facilitating bile flow to relieve cholestasis rather than suppressing its synthesis and buffering the bile (Beuers 2006). UDCA has no FXR agonist properties.

OCA is structurally related to CDCA and differs by the addition of a single ethyl group. The chemical name of OCA is 3α,7α-dihydroxy-6α-ethyl-5βcholan-24-oic acid. It is also referred to as 6α-ethylchenodeoxycholic acid, or 6-ECDCA, and as an agonist it is approximately 100-fold more potent than CDCA *in vitro* (Pellicciari 2002). OCA is also highly selective for FXR and does not bind other nuclear receptors, and with the exception of weakly activating the dedicated bile acid receptor TGR5, it does not activate any G-protein coupled receptors (CEREP 2008). OCA is in clinical development in a series of chronic liver and metabolic disease indications in which the functions regulated by FXR activation are critical etiological components.

4.3. Nonclinical Experience with Obeticholic Acid

Administration of OCA to rats (for 6 months) and dogs (for 9 months) in repeat dose toxicity trials resulted primarily in adverse effects on the liver and gastrointestinal (GI) tract at only the highest dose levels. OCA was not genotoxic in a battery of 3 genotoxicity studies. Reproductive and developmental toxicity studies in rats and rabbits demonstrated no adverse effects on fertility and embryo/fetal development at doses where OCA caused maternal toxicity.

A summary of the toxicology studies is provided in the IB. The nonclinical pharmacology experience with OCA is summarized below. For more information on the nonclinical data for OCA, please refer to the current IB.

4.3.1. Nonclinical Anti-fibrotic and Anti-inflammatory Properties

In vitro exposure of both murine and human hepatic stellate cells (HSC) to OCA represses fibrogenic α1(I) collagen and transforming growth factor-beta 1 (TGF-β1) expression by 60% to 70%, indicating that OCA is a potent regulator of HSC mediated fibrogenesis.

OCA significantly inhibits fibrogenesis and reverses liver cirrhosis, as determined by Sirius red immunostaining and morphometry in a thioacetamide (TAA)-induced liver injury model (Albanis 2005). In addition, OCA inhibits NF κB–regulated pro-inflammatory genes in hepatocytes and in vascular cells, inhibiting induction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF-α), and inflammatory mediators, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (Li 2007, Wang 2008). OCA also inhibits production of TNF-α by human peripheral blood mononuclear cells and human monocytes, and inhibits differentiation of human monocytes into dendritic cells (Gadaleta 2011). Furthermore, OCA

inhibits production of TNF-α, interleukin (IL)-17, and interferon-γ in lymphocyte-enriched human lamina propria cells (Gadaleta 2011).

4.3.2. Nonclinical Effects on Cholestasis

The results of trials performed in rodent models of cholestasis involving the administration of chemical agents that severely injure bile ducts (such as carbon tetrachloride [CCl_4] or lithocholic acid [LCA]) provide evidence that OCA is effective in preventing or reducing cholestasis *in vivo*. In the LCA model, co-infusion of OCA fully reversed the impairment of bile flow and protected against liver cell injury (Pellicciari 2002).

Results of other trials have demonstrated that OCA significantly reduces fibrotic collagen synthesis *in vitro* and in various rodent models of chronic liver injury that involve fibrosis and eventual cirrhosis, consistent with the progression of PSC (Albanis 2005, Mookerjee 2015).

4.4. Clinical Experience with Obeticholic Acid

To date, OCA has been evaluated in the clinic in a total of 25 completed and 8 ongoing trials, including patients with PBC and other chronic liver diseases (eg, portal hypertension and nonalcoholic steatohepatitis [NASH]) and healthy volunteers. Additional trials are also planned to further characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of OCA as well as the safety and efficacy of OCA in subjects with PBC and other chronic liver diseases.

As of 31 Jan 2015, approximately 1650 subjects have received at least one dose of OCA in completed or ongoing trials. Overall, the PK profile of OCA is consistent with that expected of a bile acid. Phase 1 PK trials demonstrated that OCA was rapidly absorbed and extensively conjugated with glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates were 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 peaked shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.

Phase 2 Trial 747-201 evaluated 2 doses of OCA (10 mg and 50 mg) given as monotherapy versus placebo in subjects with PBC. Significant relative and absolute reductions in 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 + 0.4% with placebo. Absolute ALP reductions were -233.5 U/L and -161.3 U/L with OCA doses of 10 mg and 50 mg, respectively compared to +11 U/L with placebo. Further, significant improvements in GGT and in conjugated bilirubin were observed with both doses compared with placebo ($p < 0.05$). OCA doses of 10 mg and 50 mg resulted in decreased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) but the change did not achieve statistical significance.

Phase 2 trial 747-202 evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects with PBC on a stable therapeutic dose of UDCA. Overall, the data from 747-202 were consistent with the monotherapy trial. Statistically significant relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p < 0.0001$). Mean ALP reductions ranged from 21% to 25% compared to 3% with placebo. Absolute ALP reductions ranged from approximately 65 U/L to 75 U/L versus 5 U/L for placebo. Significant improvements were also

seen in GGT and ALT levels with all 3 doses, in AST at 10 mg and 25 mg, and in conjugated bilirubin (% change) at 25 mg and 50 mg.

The long term safety extension (LTSE) phases of both trials (completed LTSE phase from Trial 747-202 providing exposures out to one year and ongoing LTSE phase of Trial 747-201 providing exposures up to approximately 4.5 years to date) support the long-term safety of OCA and demonstrate a durable therapeutic response.

Phase 3 Trial 747-301 evaluated 2 OCA treatment arms (10 mg and 5 mg titrating to 10 mg based on efficacy and tolerability) versus placebo in subjects with PBC on a stable therapeutic dose of UDCA or who could not tolerate UDCA. The primary efficacy endpoint was the proportion of subjects who achieved an ALP <1.67x upper limit of normal (ULN) with a minimum 15% reduction in ALP and a normal bilirubin after 12 months of treatment. Both OCA treatment groups showed statistically significant differences ($p < 0.0001$) versus placebo for the composite endpoint at all post-baseline timepoints with 47%, and 46% achieved the endpoint at 12 months in the 10 mg and titration groups compared to 10% with placebo. Consistent with the Phase 2 trials, statistically significant relative and absolute reductions in ALP were achieved in both treatment groups ($p < 0.0001$). Mean ALP reductions were 39% and 33% compared to 5% with placebo.

Overall, OCA has been demonstrated to be safe and generally well tolerated in PBC patients. The primary adverse event (AE) shown to be related to OCA is pruritus. This reflects a drug and dose related exacerbation of the most common symptom of PBC and is thought to be due to the choleretic effect of OCA that increases bile flow and hepatic clearance, but may also increase exposure to a pruritogen present in the bile that can induce pruritus in susceptible patients. Of note, UDCA therapy initiation also can induce pruritus in patients, which can be ameliorated by dose titration. Pruritus has also been observed in clinical trials with OCA in other indications, but with a much lower frequency than that observed in subjects with PBC. Other potential risks identified include liver toxicity at high doses. Detailed clinical information can be found in the OCA IB.

4.5. Summary of Known Potential Risks with Investigational Product

Investigators are referred to the current IB for a thorough presentation of the safety data associated with OCA. An overview is as follows:

Pruritus is a common symptom of chronic cholestatic diseases such as PBC and PSC. In subjects with PBC, treatment with OCA has been shown to cause a dose-dependent exacerbation of this common symptom and similar results can be expected in subjects with PSC. Pruritus has also been observed in clinical trials with OCA in other indications and in healthy volunteers, but at a lower frequency and at higher doses than that observed in subjects with chronic cholestasis. Investigator guidance for pruritus management strategies are outlined in Section 11.1.3.1 of the protocol.

Other potential risks include liver toxicity, especially at higher doses of OCA, which is consistent with nonclinical findings and the chemical characteristics of OCA as a bile acid and detergent. An increase in liver function tests and hepatobiliary AEs, including jaundice, ascites and acute cholecystitis were observed in subjects with PBC and NASH who were treated at doses that are several fold higher (primarily 20 mg to 50 mg daily) than those studied in this

protocol (1.5 mg, 3 mg, 5 mg, and 10 mg) doses. This is an important potential risk in subjects with PSC, where there is the possibility of dominant strictures of intra- and extra-hepatic bile ducts that could restrict bile flow. In order to monitor bile duct patency, the trial protocol requires that sites perform an ultrasound at Screening, at the end of the DB phase, and annually in the LTSE. Consistent with this potential risk, the present trial excludes subjects who have had, or who are suspected of having, a recent dominant stricture (Section 7.3). In addition, the trial calls for mandatory discontinuation of investigational product in those subjects whose liver chemistry (AST, ALT and or bilirubin) display clinically significant increases following the initiation of therapy (Section 7.4.1). The doses used in the present trial (1.5 mg to 10 mg) are amongst the lowest doses of OCA tested to date in a clinical setting.

Lipoprotein changes have also been observed with OCA dosing in subjects with PBC (including a decrease in high-density lipoprotein [HDL]). The clinical significance of these lipid findings remains unclear and is being studied further. Notably, despite an observed decrease in HDL levels, they generally remained within normal limits. The relevance of these findings to subjects with PSC is unclear and will be investigated further in this trial.

In addition, the Data Safety Monitoring Committee (DSMC) will review safety data from the present trial as well as other ongoing OCA trials at approximately quarterly intervals but at least every 6 months. Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability as noted in Section 6.4.3.

4.6. Rationale for Trial Design and Dose for Investigational Product

4.6.1. Rationale for Trial Design

Rationale for Treatment Indication

PSC is a rare, chronic cholestatic liver disease characterized by progressive inflammation, fibrosis, and destruction of the intrahepatic and extra-hepatic bile ducts with no identifiable cause (Eaton 2013, Hirschfield 2013). PSC disease progression can vary, but typically begins in portal tracts; fibrosis and commensurate inflammatory responses induce a progressive spread of the fibrotic condition. No treatment to date, aside from liver transplant, has been associated with an improvement in clinical outcome. As such, the unmet medical need for PSC is very high.

Drugs that can improve bile acid flow (reducing toxic bile acid concentrations in hepatocytes) and have anti-inflammatory and anti-apoptotic effects should have beneficial effects in PSC. UDCA, which is an epimer of the primary human bile acid CDCA, is often used for the treatment of PSC due to improvements in liver biochemistry following initiation of therapy. Despite general biochemical improvement, UDCA has not been shown to improve transplant free survival and, at high doses, has been associated with increased risk for serious complications (Lindor 2009). Consequently, The European Association for the Study of the Liver (EASL) does not provide a recommendation for the use of UDCA for the treatment of PSC, and The American Association for the Study of Liver Diseases (AASLD) recommends against its use (EASL 2009, Chapman 2010). However, as there are no approved drugs for the treatment of PSC, some physicians treat patients with UDCA, typically at a dose of 13 to 15 mg/kg/day.

FXR has been shown to be an essential regulator of bile acid homeostasis with its activation being associated with decreased bile acid synthesis (Lefebvre 2009). FXR is the nuclear receptor

involved in the regulation of hepatic bile acid production and flow and the modulation of hepatic inflammation, fibrosis, and regeneration. As such, FXR is a strong potential target for the treatment of cholestatic diseases such as PSC. Consistently, nonclinical models evaluating the properties of OCA have shown it to have anti-fibrotic and anti-inflammatory properties as well as being effective at reducing cholestasis (Section 4.3). Clinical data from trials in PBC showing marked reductions in liver biochemistry associated with cholestasis further support the rationale for evaluating OCA as a treatment for PSC (Section 4.4).

Rationale for Primary Efficacy Endpoint

The cholestatic conditions of PSC and PBC are both characterized by persistent increases in ALP. While UDCA did not show a treatment effect on clinical outcomes (Lindor 1997, Olsson 2005), follow up analyses showed that robust improvements in ALP, the achievement of normalized ALP levels or levels <1.5x ULN were associated with improved prognosis (Lindstrom 2013, Al Mamari 2013, Talwalkar 2013). Evaluation of OCA in PBC subjects has shown OCA to be associated with a clinically and statistically significant reduction in ALP. As such, this first trial of OCA in subjects with PSC will evaluate therapeutic response in terms of change from Baseline in ALP. Categorical improvements (ie, normalization or <1.5x ULN) will also be evaluated as secondary endpoints.

4.6.2. Rationale for Doses

This trial is intended to evaluate the safety, tolerability, and efficacy of a range of doses of OCA in subjects with PSC with an overall goal of identifying doses that are therapeutic and generally well tolerated. Patients will be randomized to 1 of 3 dose groups: 1.5 mg titrating to 3 mg OCA, 5 mg titrating to 10 mg OCA, or placebo.

While this is the first trial to evaluate OCA in subjects with PSC, the safety and tolerability of multiple doses of OCA have been established in healthy subjects and subjects with PBC (another cholestatic liver disease), at doses up to 50 mg once daily, and in subjects with alcoholic cirrhosis and portal hypertension at doses up to 25 mg. In healthy subjects, 12 days dosing of up to 100 mg per day was safe and well tolerated.

As demonstrated in the Phase 2 PBC trials, OCA can significantly reduce 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 trial 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. Starting patients on 5mg OCA and titrating to 10mg based on the clinical response appears to be an appropriate dosing strategy in patients with PBC.

Building on these data from patients with PBC, we plan to use the same titration dosing strategy for patients with PSC. This considered approach provides a means for the treating physician to carefully manage tolerability issues while still providing an opportunity for efficacy. The titration arm of 5 mg to 10 mg OCA is well-within the range shown to be safe and effective in PBC patients and in healthy volunteers. However, given the detergent properties of OCA and the potential for dominant intra- and extra-hepatic strictures that could lead to bile acid retention in subjects with PSC (Section 4.5), evaluation of additional titration arm with 1.5 mg titrating to 3 mg OCA (ie, ≤10 mg daily) is warranted.

The dose-ranging aspect of the trial design targets doses known to be therapeutic for PBC (5 mg and 10 mg), another cholestatic liver disease, but also incorporates lower doses to 1) Allow identification of the minimally safe and effective dose, and 2) Further characterize the exposure-response relationship in this patient population. The nested dose-rising approach allows for a more robust characterization of the value of titration to address potential tolerability concerns and the exposure-response relationship by addressing intra-subject variability. The nested dose-rising approach also limits the needed number to treat which is important given the rarity of the disease and limited pool of patients from which to recruit, and minimizes the number of patients unnecessarily exposed to study medication.

Rationale for Placebo

There are no approved therapies for the treatment of PSC that could be used as an active control. As such, the use of a placebo control is warranted to maintain the study blind and scientific validity of the trial. UDCA is used by some physicians due to associated improvements in liver biochemistry. However, EASL does not provide a recommendation regarding UDCA use in PSC, and AASLD recommends against its use (EASL 2009, Chapman 2010). Based on this guidance, UDCA would not be an appropriate active control. However, the Sponsor does recognize that UDCA is used in this orphan disease, and patients who are currently taking UDCA may be eligible to participate in the trial (Section 7.2). Subjects will be stratified by the presence or absence of UDCA use, then randomized, in equal proportions, to each of the treatment groups (Section 8.4.1).

Rationale for Duration of Dosing

In the Phase 2 PBC trials with OCA, the double-blind (DB) evaluation of the reduction in ALP associated with OCA treatment was evaluated over 85 days. Significant reductions in ALP were observed as early as 2 to 4 weeks with maximal reductions (at a single dose level) apparent by 8 weeks. Due to similarities in the cholestatic etiology of PSC and PBC, it is anticipated that a similar evaluation period will be sufficient to evaluate OCA in PSC. As such, the present trial will evaluate each dose over 12 week periods.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

To evaluate the effects of OCA on the following in subjects with PSC:

- Serum ALP
- Safety

5.2. Secondary Objectives

The secondary objectives are to evaluate the effects of OCA on the following in subjects with PSC:

- Hepatic biochemistry and indices of function
- Markers of:
  - Hepatic fibrosis and GI inflammation and disease
  - FXR activity
  - Inflammatory bowel disease (IBD)
- PK of OCA and other bile acids
- Exposure response of total OCA (OCA and its conjugates) to biomarkers eg, ALP and bile acids
- Long-term efficacy and safety of OCA
- Disease-specific symptoms

6. INVESTIGATIONAL PLAN

6.1. Overall Trial Design

Double-blind phase (DB)

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-finding evaluation of the efficacy and safety of OCA in subjects with PSC. The trial design is shown in Figure 1 and the schedule of trial procedures for the DB phase is presented in Table 1. Approximately 75 subjects who provide written informed consent and meet all of the inclusion and none of the exclusion criteria will be randomized to 1 of 3 treatment groups as follows: 1.5 mg titrating to 3.0 mg OCA, 5 mg titrating to 10 mg OCA, or placebo in a 1:1:1 ratio. Subjects will administer investigational product orally, once daily for 2 consecutive 12-week periods.

For the first 12 weeks after randomization, the subject's dose will be 1.5 mg OCA, 5 mg OCA, or placebo. After 12 weeks, the subject's dose will be titrated as detailed in Section 6.4.1 and DB treatment will continue for a further 12 weeks at that dose.

Randomization will be stratified by the presence or absence of concomitant UDCA use and total bilirubin level (≤1.5x ULN or >1.5x ULN but <2.5x ULN).

Long-Term Safety Extension Phase (LTSE)

Following completion of participation in the DB phase, subjects will be asked to reconfirm their consent for participation in the LTSE phase (a further 24 months). The schedule of trial procedures for the LTSE is shown in Table 2.

Upon a subject's completion of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA unless safety and tolerability warrant a dose reduction to 5 mg. The titration schedule and options for the LTSE phase are detailed in Section 6.4.2. If an Investigator does not wish for a subject to be titrated in line with Table 4, this may be discussed with the Medical Monitor.

6.1.1. Trial Design Diagram

Figure 1: Trial Design Schematic

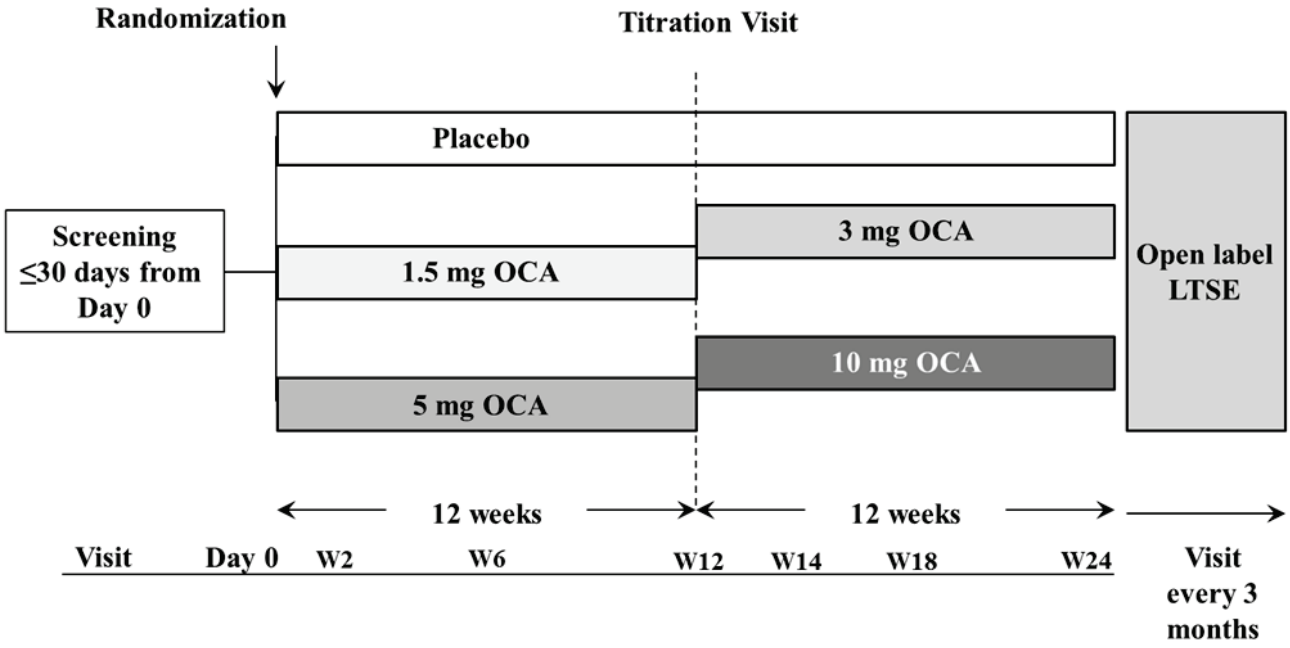


Table 1: Schedule of Trial Procedures: Double-Blind Phase

Visit Type[a]	**Screening (Day -30 to Day -1)**	**Day 0**[b]	**Visit W2**	**Visit W6**	**Visit W12**[c]	**Visit W14**	**Visit W18**	**Visit W24**[d]**/ LTSE D1/ EOT**[e]	**FU (4 wks)**[f]
Visit Window[g]	≤30d		±3d	±1wk	±1wk	±1wk	±1wk	±1wk	±1wk
Informed Consent	X								
Medical History	X								
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X							
Physical Exam	X[h]							X	
Vital Signs[i]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X							X	
Transient Elastography[j]		X						X	
Hepatic Ultrasound[k]	X							X	
Partial Mayo Score[l,m]	X	X	X	X	X	X	X	X	X
CDAI[m,n]	X	X	X	X	X	X	X	X	X
Pruritus VAS and 5-D[o]		X	X	X	X	X	X	X	X
Subject Research Questionnaire[o]								X	
Adverse Events		X[p]	X	X	X	X	X	X	X
Randomization		X							

Table 1: Schedule of Trial Procedures: Double-Blind Phase (Continued)

Visit Type[a]	**Screening (Day -30 to Day -1)**	**Day 0**[b]	**Visit W2**	**Visit W6**	**Visit W12**[c]	**Visit W14**	**Visit W18**	**Visit W24**[d]**/ LTSE D1/ EOT**[e]	**FU (4 wks)**[f]
Visit Window[g]	≤30d		±3d	±1wk	±1wk	±1wk	±1wk	±1wk	±1wk
Dispense Investigational Product		X[q]			X			X[r]	
Investigational Product Accountability/ Compliance[s]			X	X	X	X	X	X	
Laboratory Evaluations[t]									
Serum Chemistry, Hematology, & Coagulation Parameters	X[u]	X	X	X	X	X	X	X	X
FGF-19		X			X			X	
CRP		X			X			X	
ELF Markers & Other Analytes[v]		X			X			X	
Plasma Bile Acids		X			X			X	
C4		X			X			X	
PK[w]					X			X	
Apolipoprotein & NMR Lipoprotein Panel		X			X			X	
Dipstick Urinalysis	X	X			X			X	
Urine Pregnancy Test[x]	X	X			X			X	X
Fecal Sample[y]		X			X			X	
Genetics Study[z]		X						X	

[a] Subjects must be fasted prior to all clinic visits (except Screening) and investigational product should not be administered prior to clinic visits (see Section 8.1).
[b] Day 0 must occur by Day 31 for a subject to be eligible to continue in the trial.
[c] Week 12 is the Dose Titration visit.
[d] The Week 24 visit is the final visit during the DB treatment period. For subjects who continue into the LTSE, the Week 24 visit is also Day 1 of the LTSE, and unblinding occurs after the Week 24/LTSE Day 1 procedures have been completed (except dispensing of open-label investigational product).
[e] End of treatment (EOT) visit is completed for any randomized subject who discontinues the study prior to reaching Week 24 of the DB phase; this should occur as close as possible to the final dose of investigational product. If a subject discontinues on the day of a scheduled trial visit, the procedures from the scheduled visit will be recorded as EOT in the CRF.
[f] Follow-Up visit: If a subject discontinues the study prior to the end of Week 24 or does not proceed into the LTSE, he/she returns to the site for a Follow-Up visit, which should occur 4 weeks (±1 week) after her/his last dose of investigational product.
[g] Timing of all visits is relative to Day 0.
[h] Height is measured at the Screening visit only.
[i] Vital signs: oral temperature, sitting heart rate (HR), respiratory rate, and sitting blood pressure ([BP] systolic and diastolic). When taking HR, respiratory rate, and BP readings, subjects should be seated quietly for a minimum of 3 minutes before the readings are taken.
[j] TE: at trial sites where the Fibroscan® TE device is available. TE has a 5-day visit window. For the Day 0 assessment, TE should occur either on Day 0 or within 5 days prior to Day 0. For the Week 24 assessment, the TE should occur within ±5 days of the onsite visit if it is not possible to schedule the TE on the same day as that visit, but the visit(s) should remain within the overall visit window.
[k] Hepatic ultrasound has a ±5-day visit window (ie, if it is not possible to schedule the ultrasound on the same day as the onsite visit, it may occur within 5 days on either side of the visit, but the visit(s) should remain within the overall visit window).
[l] Partial Mayo score completed only for subjects with UC.
[m] Subjects with UC will be asked to complete a diary the day prior to their next trial visit, recording details since their last scheduled visit. Subjects with CD should complete the diary in the 7 days prior to their next clinic visit. Diary card data from the Screening period are collected at the Day 0 visit.
[n] CDAI completed only for subjects with CD.
[o] Questionnaire completed by the subject.
[p] Adverse events will be collected from the time that signed informed consent is obtained.
[q] All subjects are instructed to administer the first dose of investigational product on Day 1 and at approximately the same time of day for the duration of the trial (see Section 8.1).
[r] Investigational product is dispensed only for subjects who continue into the LTSE. (Dispensing of open-label investigational product occurs after completion of the Week 24/LTSE Day 1 procedures and the subsequent unblinding of the subject's treatment allocation.)
[s] Investigational product accountability/compliance will include review of tablets and bottles dispensed and returned at each clinic visit
[t] All laboratory samples (except urine and serum pregnancy test, if applicable) are analyzed by the Central Laboratory.
[u] IgG4 is included in the assessment panel at Screening only.
[v] Other analytes includes an additional blood sample for exploratory analysis.
[w] PK samples will be collected from those subjects who have consented for PK sampling procedures. Please refer to Section 10.5 for a schedule of sampling.
[x] For female subjects of child bearing potential, a urine β-hCG test is used. If the urine test is positive, it is to be repeated as a serum pregnancy test. See Section 7.1 for procedures to be followed for a subject whose pregnancy is early terminated and wishes to continue in the trial.
[y] Fecal sample: for measurement of calprotectin and gut fecal microbiome; provision of a fecal sample by subjects is not mandatory. The subject should be instructed to collect a fecal sample within 2 days of the scheduled visit, as described in the laboratory manual.
[z] Genetics study: blood samples will be collected from those subjects who have consented for RNA sampling procedures.

Table 2: Schedule of Trial Procedures: LTSE Phase

Visit Type[a,b]	**LTSE D1/DB Visit W24**[c]	**Contact W2**	**Visit M3**	**Visit M6**	**Visit M9**	**Visit M12**	**Visit M15**	**Visit M18**	**Visit M21**	**Visit M24/ EOT**[d]	**FU**[e] **(4 wks)**
Visit Window[f]	±1wk	±3 d	±2wk	±2wk	±2wk	±2wk	±2wk	±2wk	±2wk	±2wk	±1wk
Safety Contact[g]		X									
Concomitant Medication Review	X		X	X	X	X	X	X	X	X	X
Physical Exam	X									X	
Vital Signs[h]	X		X	X	X	X	X	X	X	X	X
12-Lead ECG	X									X	
Transient Elastography[i]	X					X				X	
Hepatic Ultrasound[j]	X					X				X	
Partial Mayo Score[k,l]	X		X	X	X	X	X	X	X	X	X
CDAI[l,m]	X		X	X	X	X	X	X	X	X	X
Pruritus VAS and 5-D[n]	X		X	X	X	X	X	X	X	X	X
Subject Research Questionnaire[n]	X									X	
Adverse Events	X		X	X	X	X	X	X	X	X	X
Dispense Investigational Product	X[o]		X	X	X	X	X	X	X		
Investigational Product Accountability/ Compliance[p]	X		X	X	X	X	X	X	X	X	

Table 2: Schedule of Trial Procedures: LTSE Phase (Continued)

Visit Type[a,b]	LTSE D1/DB Visit W24[c]	Contact W2	Visit M3	Visit M6	Visit M9	Visit M12	Visit M15	Visit M18	Visit M21	Visit M24/ EOT[d]	FU[e] (4 wks)
Visit Window[f]	±1wk	±3 d	±2wk	±2wk	±2wk	±2wk	±2wk	±2wk	±2wk	±2wk	±1wk
Laboratory Evaluations[q]											
Serum Chemistry, Hematology, & Coagulation Parameters	X		X	X	X	X	X	X	X	X	X
FGF-19	X					X				X	
CRP	X			X		X		X		X	
ELF Markers & Other Analytes[r]	X					X				X	
Plasma Bile Acids & C4	X			X		X				X	
PK[s]	X										
Apolipoprotein & NMR Lipoprotein Panel	X										
Dipstick Urinalysis	X			X		X		X		X	
Urine Pregnancy Test[t]	X		X	X	X	X	X	X	X	X	X
Fecal Sample[u]	X					X				X	
Genetics Study[v]	X					X				X	

[a] Subjects must be fasted prior to all clinic visits and investigational product should not be administered prior to clinic visits (see Section 8.1).

[b] If the Investigator is planning on up-titrating a subject at an LTSE visit, the subject needs to return for an additional Pre-Titration visit, approximately 1 week prior to the scheduled LTSE visit to enable blood to be taken for laboratory sample analysis. The subject then attends for the scheduled 3 month visit. Subjects experiencing significant AEs (eg, severe pruritus) or other symptoms that are not tolerated, may not be eligible for titration. After any increase in OCA dose, the Investigator or designee should contact the subject approximately 2 weeks following the titration visit to assess for AEs and to verify that the subject is dosing as directed.

[c] The LTSE D1 is also the final visit (Week 24) of the DB treatment period. For subjects continuing into the LTSE, unblinding occurs after the Week 24/LTSE Day 1 procedures have been completed (except dispensing of open-label investigational product).

[d] End of treatment (EOT) visit is completed for any randomized subject who discontinues the LTSE prior to reaching Month 24; this should occur as close as possible to the final dose of investigational product. If a subject discontinues on the day of a scheduled trial visit, the procedures from the scheduled visit will be recorded as EOT in the CRF.

[e] Follow-Up visit: If a subject discontinues the LTSE prior to the end of Month 24, he/she returns to the site for a Follow-Up visit, which should occur 4 weeks (±1 week) after his/her last dose of investigational product.
[f] Timing of all visits is relative to LTSE Day 1.
[g] The Safety Contact can be either via telephone or email, and does not require an onsite visit.
[h] Vital signs: oral temperature, sitting HR, respiratory rate, and sitting BP (systolic and diastolic). When taking HR, respiratory rate, and BP readings, subjects should be seated quietly for a minimum of 3 minutes before the readings are taken.
[i] TE: at trial sites where the Fibroscan® TE device is available. The TE should occur within ±5 days of the onsite visit if it is not possible to schedule the TE on the same day as that visit, but the visit(s) should remain within the overall visit window.
[j] Hepatic ultrasound has a ±5-day visit window (ie, if it is not possible to schedule the ultrasound on the same day as the onsite visit, it may occur within 5 days on either side of the visit, but the visit(s) should remain within the overall visit window).
[k] Partial Mayo score completed only for subjects with UC.
[l] Subjects with UC will be asked to complete a diary the day prior to their next trial visit, recording details since their last scheduled visit. Subjects with CD should complete the diary in the 7 days prior to their next clinic visit.
[m] CDAI completed only for subjects with CD.
[n] Questionnaire completed by the subject.
[o] Investigational product is dispensed only for subjects who continue into the LTSE. (Dispensing of open-label investigational product occurs after completion of the Week 24/LTSE Day 1 procedures and the subsequent unblinding of the subject's treatment allocation.)
[p] Investigational product accountability / compliance will include review of tablets and bottles dispensed and returned at each clinic visit.
[q] All laboratory samples (except urine and serum pregnancy test, if applicable) are analyzed by the Central Laboratory.
[r] Other analytes includes an additional blood sample for exploratory analysis.
[s] PK samples will be collected from those subjects who have consented for PK sampling procedures. Please refer to Section 10.5 for a schedule of sampling.
[t] For female subjects of child bearing potential, a urine based β-hCG test is used. If the urine pregnancy test is positive, the test is to be repeated as a serum pregnancy test. See Section 7.4.1 for procedures to be followed for a subject whose pregnancy is early terminated and wishes to continue in the trial.
[u] Fecal sample: for measurement of calprotectin and gut fecal microbiome; provision of a fecal sample by subjects is not mandatory. The subject should be instructed to collect a fecal sample within 2 days of the scheduled visit, as described in the laboratory manual.
[v] Genetics study: blood samples will be collected from those subjects who have consented for RNA sampling procedures.

6.1.2. Trial Duration

Table 3: Planned Duration of Trial Phases

DB Phase	
Time expected for all subjects to be enrolled	Approximately 18 months
Duration of individual subject participation	Up to 7 months (including screening)
LTSE	
Duration of individual subject participation	Up to 24 months
DB Phase & LTSE	
Total duration of the trial (first subject consented to last subject completing last study visit)	Approximately 50 months

The LTSE may be extended on an annual basis beyond 24 months and this will be determined by the Sponsor. Prior to any extension of the LTSE, the protocol will be amended and submitted for regulatory and Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval.

6.2. Number of Subjects

Approximately 75 subjects who meet eligibility criteria will be included in the trial.

6.3. Treatment Assignment

Eligible subjects will be randomized to 1 of 3 treatment groups and will initiate treatment with 1.5 mg OCA, 5 mg OCA, or matching placebo. Randomization will be in accordance to a 1:1:1 ratio (ie, 25 subjects/group).

Subjects will be stratified by the presence or absence of concomitant UDCA use and total bilirubin level at Screening, according to defined stratification criteria (Section 8.4.1) and then randomized in equal proportions to each of the treatment groups.

6.4. Dose Adjustment Criteria and Dose Titration

6.4.1. Double-Blind Phase

Following randomization, subjects will administer the assigned, blinded treatment once daily for 12 weeks.

After 12 weeks, the subject's dose will be titrated as follows, providing there are no limiting safety or tolerability concerns in the opinion of the Investigator, while maintaining the trial blind: the 1.5 mg OCA treatment group will titrate to 3 mg, the 5 mg OCA treatment group will titrate to 10 mg OCA, and the placebo group will remain on placebo. DB treatment will continue for a further 12 weeks at that dose.

Any subjects whose dose is not titrated, due to safety or tolerability concerns, will remain on their starting treatment (1.5 mg OCA, 5 mg OCA, or placebo) for the remainder of the DB phase to Week 24.

6.4.2. LTSE Phase

Upon a subject's completion of the Week 24 visit, at the end of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA (Table 4) unless safety and tolerability warrant a dose reduction to 5 mg.

Table 4: Initial LTSE Doses of OCA

Investigational Product at End of DB Phase (once daily)	Investigational Product at Start of LTSE (once daily)
Placebo	5 mg OCA
3 mg OCA	5 mg OCA
10 mg OCA	10 mg OCA

Those subjects who did not up-titrate their dose at Week 12 in the DB phase can remain on their DB dose as indicated in Table 5, or commence at 5 mg at the decision of the Investigator based on safety and tolerability of the DB dose at Week 24.

Table 5: Initial LTSE Doses of OCA for Non-Titrating Subjects

Investigational Product at End of DB Phase (once daily)	Investigational Product at Start of LTSE (once daily)
1.5 mg OCA	1.5 mg OCA
5 mg OCA	5 mg OCA

If an Investigator does not wish for a subject to be titrated in line with the above schedules, this may be discussed with the Medical Monitor.

During the LTSE phase subjects may titrate to higher doses of OCA, at a frequency not greater than 3 monthly (ie, at each of the scheduled visits), up to a maximum dose of 10 mg daily. The guideline for an increase in the dose of open-label OCA is based on the goal of achieving ALP <1.5x ULN and tolerability. Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg. Intermediate doses (eg, 6.5 mg) may be considered as deemed appropriate by the Investigator. Dose should not exceed 10 mg.

The Investigator may decrease the dose of OCA, or dosing frequency, in line with safety and tolerability as required for that subject. Following a change in OCA dose or dose frequency, an Investigator may be permitted to return the subject to a prior dose or dosing frequency and this should be discussed with the Intercept Medical Monitor in advance.

6.4.3. Safety Criteria for Adjustment or Stopping Doses

The Data Safety Monitoring Committee (DSMC) will review safety data from this trial as well as other ongoing OCA trials at approximately quarterly intervals but at least every 6 months. Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC

evaluation of OCA safety and tolerability. At a minimum, the occurrence of 2 life threatening serious adverse events (SAEs) or an SAE resulting in death will trigger an unscheduled and unblinded review of the data by the DSMC to determine if the trial should continue. Section 6.5 details the criteria for trial termination. Reasons for discontinuation of individual subjects are noted in Section 7.4.1 and Section 7.4.2.

6.5. Criteria for Trial Termination

The Sponsor reserves the right to terminate the trial at any time. Additionally, it is agreed that, for reasonable cause, the Investigator may terminate the trial at his/her site at any time.

It is normal procedure to review the emerging safety data. As a result of such a review or a recommendation by the DSMC, it may be necessary to stop the trial before all subjects have completed the trial. In addition, the Sponsor may terminate the trial at an investigational site at any time (eg, due to the quality of data), as determined by the number of subjects enrolled or the quality of the data from the site.

The Investigator and/or Sponsor (or designee) must notify the IRB/IEC of discontinuation of a site or the trial and the reason for doing so. Local requirements for notification of trial termination will be adhered to.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Population

Approximately 75 subjects with PSC will be randomly assigned to treatment groups using an interactive web response system (IWRS). Up to 50% of the trial population may be taking concomitant UDCA. Once this cap is reached, only those subjects who have not been treated with UDCA for at least 3 months prior to and including Day 0 may be enrolled. In addition, a maximum of 25% of enrolled subjects will have a total bilirubin between >1.5x ULN and <2.5x ULN at Screening. Prospective subjects will be identified primarily from the hospital and/or physician's database of PSC subjects, or may be referred from other physicians. Subjects may self-refer themselves to an Investigator if they become aware of the trial through local, national or international PSC patient societies, forums and networks or websites (eg, www.clinicaltrials.gov).

7.2. Subject Inclusion Criteria

Subjects must meet all of the following to be eligible to participate:

1. Male or female aged 18 to 75 years
2. Must provide written informed consent and agree to comply with the trial protocol
3. Must have a diagnosis of PSC (based on cholangiography at any point in time)
4. ALP at Screening ≥2x ULN.

5. Total bilirubin at Screening <2.5x ULN.

   Note 1: Subjects will be stratified according to total bilirubin level and no more than 25% of subjects recruited will have a total bilirubin >1.5x ULN and <2.5x ULN at Screening.

6. For subjects with concomitant IBD:

   a. Colonoscopy (if subject has a colon) or other appropriate endoscopic procedure within 12 months of Day 0 confirming no dysplasia or colorectal cancer
   b. Subjects with Crohn's Disease (CD) must be in remission as defined by a Crohn's Disease Activity Index (CDAI) <150.
   c. Subjects with ulcerative colitis (UC) must either be in remission or have mild disease. Remission is defined as a partial Mayo score of ≤2 with no individual sub-score exceeding 1. Mild disease is defined as a partial Mayo score ≤3 with no individual sub-score exceeding 1 point.

7. For subjects being administered UDCA as part of their standard of care the dose must have been stable for ≥3 months prior to, and including, Day 0 and must not have exceeded 20 mg/kg/day during this time.

   Note 2: Subjects not taking UDCA at Day 0 must not have taken UDCA for ≥3 months prior to, and including, Day 0 and must not take UDCA during the DB period. Subjects will be stratified according to UDCA use, and no more than 50% of subjects administering UDCA at Day 0 will be enrolled.

8. Subjects being administered biologic treatments (eg, anti-TNF or anti-integrin monoclonal antibodies), immunosuppressants, systemic corticosteroids, or statins, must have been on a stable dose for ≥3 months prior to, and including, Day 0 and should plan to remain on a stable dose throughout the trial.

9. Contraception: female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the trial and until 4 weeks following the last dose of investigational product (including LTSE doses). Effective methods of contraception are considered to be those listed below:

   - Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm with spermicide; or
   - Intrauterine device; or
   - Vasectomy (partner), or
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence, if in line with the preferred and usual lifestyle of the subject [where abstinence is defined as refraining from heterosexual intercourse during the trial duration (from first administration of investigational product until 4 weeks after the last dose of investigational product)]

7.3. Subject Exclusion Criteria

Subjects will be excluded from trial participation if they meet any of the following:

1. Evidence of a secondary cause of sclerosing cholangitis at Screening
2. Immunoglobulin G4 (IgG4) >4x ULN at Screening or evidence of IgG4 sclerosing cholangitis
3. Small duct cholangitis in the absence of large duct disease
4. Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including:
   - Current Child-Pugh classification B or C
   - History of, or current diagnosis or suspicion of, CCA or other hepatobiliary malignancy, or biliary tract dysplasia.
   - History of liver transplantation, or current model of end stage liver disease (MELD) score ≥12
   - History of, or current, cirrhosis with complications, including history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma, or hepatic encephalopathy (as assessed by the Investigator)
   - Current known portal hypertension with complications, including known gastric or large esophageal varices, poorly controlled or diuretic resistant ascites, history of variceal bleeds, or related therapeutic or prophylactic interventions (eg, beta blockers, insertion of variceal bands or transjugular intrahepatic portosystemic shunt [TIPS])
   - History of, or current, hepatorenal syndrome (type I or II) or Screening serum creatinine >2 mg/dL (178 μmol/L)
   - Platelet count <50 $x10^9$/L
5. Current clinical evidence of dominant strictures that are considered clinically relevant in the opinion of the Investigator or current biliary stent at Screening
6. Current cholecystitis or evidence of current biliary obstruction due to gallstones. Asymptomatic gallstones that are not considered a safety risk in the opinion of the Investigator might be acceptable subject to discussion and agreement with the Medical Monitor
7. Colonic dysplasia within ≤5 years prior to Day 0
8. History of any small bowel resection.
9. History of other chronic liver diseases, including, but not limited to, PBC, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA), hepatitis C virus, and overlap syndrome
10. Known Gilbert's syndrome or history of elevations in unconjugated (indirect) bilirubin >ULN or unconjugated (indirect) bilirubin >ULN at Screening

11. Known history of human immunodeficiency virus (HIV) infection
12. Currently experiencing, or experienced within ≤3 months of Screening, pruritus requiring systemic or enteral treatment.
13. Known or suspected acute cholangitis in the 3 months prior to, and including, Day 0 including cholangitis treated with antibiotics
14. Administration of antibiotics is prohibited ≤1 month of Day 0 (unless subject is on a stable prophylaxis dose for at least 3 months prior to Day 0).
15. Administration of the following medications is prohibited ≤6 months of Day 0 and throughout the trial: fenofibrate or other fibrates and potentially hepatotoxic medications (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
16. IBD flare during Screening (up to and including Day 0), where "flare" is defined as follows:
    - UC flare: partial Mayo Score ≥5, and
    - CD flare: CDAI ≥250
17. Evidence of deleterious effects of alcohol abuse (as assessed by the Investigator) or excessive alcohol consumption (>4 units/day for males, >2 units/day for females)
18. Known or suspected use of illicit drugs or drugs of abuse (allowed if medically prescribed or indicated) within 3 months of Day 0
19. If female: known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
20. Other concomitant disease, malignancy, or condition likely to significantly decrease life expectancy to less than the duration of the trial (eg, moderate to severe congestive heart failure)
21. Participation in another investigational drug, biologic, or medical device trial within 30 days prior to Screening
22. History of noncompliance with medical regimens, or subjects who are considered to be potentially unreliable
23. Blood or plasma donation within 30 days prior to Day 0
24. Mental instability or incompetence such that the validity of informed consent or compliance with the trial is uncertain.

7.4. Subject Withdrawal Criteria

7.4.1. Reasons for Mandatory Investigational Product or Trial Discontinuation

Pregnancy of a Female Subject

If a female subject becomes pregnant, she must stop investigational product administration immediately and be withdrawn from the trial. The subject must be followed by the Investigator through the pregnancy outcome. The mother and infant will be followed as considered appropriate by the Investigator and the Intercept Medical Monitor.

The Investigator must contact the Intercept Medical Monitor and discuss, in advance, any subject whose pregnancy is early terminated and would like to continue to participate in the trial. A minimum requirement for allowing the subject to restart dosing is documentation of a negative serum beta human chorionic gonadotrophin (β-hCG) test. However, this is not in and of itself a guarantee for being allowed to continue in the study. For reporting purposes, pregnancy is not considered a SAE but is reported on the Pregnancy Notification Form (see Section 11.1.9).

Clinical Laboratory Values

Development of the following clinical laboratory values, without explanation, during the course of the DB and LTSE phases of the trial mandates investigational product discontinuation:

- AST and/or ALT >3x ULN **AND** 2x the Baseline value **OR**
- Two consecutive measurements of total bilirubin >ULN **AND** >2x the Baseline value in the absence of evidence of new biliary obstruction.

The term "Baseline" within this protocol, unless otherwise specified, is intended to mean, "pretrial" or "pretreatment" (of investigational product). It refers to values obtained during the Screening, retests, or Day 0 visits, prior to the subject's first dose of investigational product.

If a subject is required to discontinue investigational product due to an increase in AST, ALT, or bilirubin, the subject must be followed at appropriate intervals until these parameters have returned to within the normal range or pretrial values, and/or are stable or there is are stable, or there is no ongoing clinical concern.

IBD Flares

Subjects who experience 3 or more IBD flare-ups in one year during the study will be discontinued, where "flare" is defined as follows:

- For UC flare: as a partial Mayo Score ≥5, and
- For CD flare: as a CDAI ≥250

Section 7.4.2 below describes treatment guidelines for managing IBD flares during the study.

7.4.2. Other Reasons for Study Discontinuation

A subject should be discontinued from the study if:

- The subject decides that it is in his/her best interest. It is fully understood that all subjects volunteer for the trial and that they may withdraw their consent to continue in the trial at any time.
- The Investigator considers that it is advisable or in the best interest of the subject.
- There is a major violation of the clinical trial protocol for the subject that would jeopardize the subject's safety and/or data quality.
- There is significant noncompliance of the subject that would jeopardize the subject's safety and/or data quality.

- The development of any exclusion criteria (see Section 7.3) that would jeopardize the subject's safety and/or data quality.
- The subject is consistently unable to provide blood or urine samples.
- There is an occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important, such that they would jeopardize the subject's safety.

A reasonable effort must be made to determine the reason(s) why a subject fails to return for his/her final visit or is discontinued from the trial. This information and date must be recorded on the appropriate case report form (CRF).

Bacterial Cholangitis

It is anticipated that 10% to15% of subjects may experience bacterial cholangitis at some point during participation in the trial (Lee 2002). Bacterial cholangitis is generally associated with elevation of serum bilirubin, ALP, and transaminases in conjunction with clinical signs and symptoms and positive diagnostic imaging tests. Local guidelines should be followed for the management of patients with acute bacterial cholangitis. In the absence of such local guidelines, the following guidelines should be followed if acute cholangitis is suspected:

- Diagnosis of acute cholangitis should be established based on a combination of typical clinical features, laboratory data, and imaging findings. Subsequent to an intervention to relieve biliary obstruction acute cholangitis may occur with typical signs and symptoms including intermittent fever with chills, right upper quadrant pain, and jaundice (also known as the Charcot triad). Further confirmation of the diagnosis should then be made via laboratory data (eg, elevated C-reactive protein levels and/or leukocytosis) and abdominal imaging tests (magnetic resonance cholangiopancreatography).
- Treatment of acute cholangitis should be directed towards treatment of the biliary infection and relieving obstruction. Therefore, treatment is comprised of systemic antibiotic therapy and biliary drainage procedures, with appropriate supportive care.
- Antibiotic agents should be administered empirically as early as possible. Blood and bile cultures should also be performed at the earliest opportunity and prior to initiating antibiotic treatment, if possible.
- The selection of an antibiotic agent should be based on likely infecting bacteria, the severity of the disease, and the presence of comorbidities. Empiric antibiotic agents may be replaced by directed therapies once the blood and bile culture results become available. The use of amoxicillin/clavulanate and other antibiotic treatments with potential for hepatotoxicity should be avoided.

Investigational product may be interrupted at the discretion of the Investigator. Discontinuation from the trial is not mandatory in cases of bacterial cholangitis unless signs and symptoms do not resolve within a clinically reasonable timeframe (typically within 1 month or as agreed upon with the Medical Monitor) or the cholangitis becomes life-threatening in the opinion of the Investigator or Medical Monitor. In any event, investigational product should not be restarted until signs and symptoms have resolved and the subject's liver biochemistry has returned to pre-cholangitis levels.

A subject with ≥3 bacterial cholangitis events in one year during the study should be discontinued from the trial.

IBD Flare

If a subject experiences an IBD flare during the trial (post-Day 0), he/she may remain on investigational product but this should be discussed with the Medical Monitor and IBD flares should be treated as follows (but adjusted based upon local guidelines and standards of care, disease severity and personal patient preferences, as appropriate): aminosalicylates alone (high dose if appropriate) or with a topical aminosalicylate and/or topical, oral, or intravenous corticosteroids or immunosuppressant therapy, including anti-TNF therapy. Surgery may be required in severe cases that are refractory to medicinal treatment.

Subjects who experience 3 or more IBD flare-ups in 1 year during the study will be discontinued.

Bile Duct Stricture

Investigational product may be interrupted at the discretion of the Investigator if a subject develops a stricture requiring intervention (eg, drainage, ERCP, stent) in order to re-establish bile flow. If the investigational product has been interrupted and the subject does not show improvement within 1 month of treatment, further evaluation by the Investigator and discussion and agreement with the Medical Monitor is required before a subject is considered eligible to resume investigational product administration or to continue in the trial.

Pruritus

Pruritus is a common symptom in PBC but less common in PSC (Chapman 2011). Investigator guidance for pruritus management strategies are outlined in Section 11.1.3.1 of this protocol. Subjects who experience one or more episodes of severe pruritus that are not tolerable based on Investigator assessment, despite optimal supportive treatment as outlined in Section 11.1.3.1, should be discontinued from the trial.

7.4.3. Subject Discontinuation Notification

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

If a subject is withdrawn from either the DB phase or the LTSE phase of the trial early (regardless of the cause), all of the End of Treatment (EOT) evaluations are to be performed at the time of withdrawal, and as close as possible to the administration of the last dose of investigational product, to the extent possible.

8. TREATMENT OF SUBJECTS

8.1. Investigational Product Treatment Regimen

Subjects enrolled in the trial will be treated with OCA and/or placebo. On Day 0, subjects will be randomized to one of the following treatments: placebo, 1.5 mg OCA, or 5 mg OCA. Because there are 2 different sizes of tablet used in this trial (1.5 mg OCA tablet and matching placebo are smaller than the 5 mg OCA and matching placebo), in the DB phase all subjects randomized to receive OCA will be administered with both OCA and placebo tablets, whereas subjects randomized to placebo will receive only placebo tablets (ie, a double-dummy approach). In order to maintain the blind, the daily treatment regimen for each effective dose is shown in Table 6. At the Week 12 titration visit, placebo subjects will remain on placebo tablets only, the 1.5 mg OCA dosing group will be increased to a daily dose of 3 mg OCA, and the 5 mg dosing group will be increased to a daily dose of 10 mg OCA. The trial blinding will be maintained during this process. Any subject whose dose is not titrated, due to safety or tolerability concerns, will remain on their starting treatment (1.5 mg OCA, 5 mg OCA, or placebo) for the final 12 weeks of the DB phase.

Investigational product will be dispensed in bottles of 100 tablets, and subjects will be instructed to take the number of tablets indicated by their treatment group. During the first 12 weeks of the DB phase, subjects will be instructed to administer 2 tablets daily with water: one 1.5 mg (small) tablet and one 5 mg (big) tablet. During weeks 12 through 24 of the DB phase, subjects will be instructed to administer four tablets daily: two 1.5 mg (small) tablets and two 5 mg (big) tablets.

During the LTSE subjects will administer open-label OCA as described in Section 6.4.2 and Table 6, below.

All subjects will administer the first dose of investigational product on Day 1, and investigational product is to be administered at approximately the same time of day throughout the duration of the trial. On trial visit days, subjects who usually administer investigational product in the morning should wait until after they have completed their trial visit and blood draws before taking their investigational product.

Subjects are instructed that their last dose of investigational product will be administered on the day prior to their LTSE Month 24 visit.

Table 6: Daily Tablet Regimen by Treatment Group

Effective Dose	1.5 mg OCA Tablet	1.5 mg Placebo Tablet	5 mg OCA Tablet	5 mg Placebo Tablet
DB Phase After Day 0				
Placebo	-	1	-	1
1.5 mg OCA	1	-	-	1
5 mg OCA	-	1	1	-
DB Phase After Week 12				
Placebo	-	2	-	2
3 mg OCA	2	-	-	2
10 mg OCA	-	2	2	-
LTSE				
1.5 mg OCA	1	-	-	-
3 mg OCA	2	-	-	-
5 mg OCA	-	-	1	-
10 mg OCA	-	-	2	-

8.2. Concomitant Medications

Relevant information about all concomitant drugs (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of Screening) and during the trial must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the trial.

8.2.1. Ursodeoxycholic Acid

Subjects taking UDCA at Day 0 should maintain this dose and the timing of administration of UDCA for the duration of the DB phase of the trial (24 weeks). Subjects who are not taking UDCA on entry into the trial should not initiate UDCA therapy at any time during their participation in the DB phase of the trial.

During the LTSE phase, UDCA may be used as considered clinically appropriate, provided the dose of UDCA does not exceed 20 mg/kg/day.

8.2.2. Bile Acid Sequestrants

While systemic or enteral therapy for pruritus is an exclusion criterion at trial entry, the treatment of pruritus during the trial is permitted if required.

Bile acid sequestrants (BAS), aluminium hydroxide, or smectite-containing antacids should be administered at least 4 hours apart from investigational product (ie, they should be used 4 hours prior to or 4 hours after investigational product administration).

In addition, BAS, aluminium hydroxide, or smectite-containing antacids should be administered at least 4 hours apart from UDCA (ie, they should be used 4 hours prior to or 4 hours after UDCA administration).

8.2.3. Prohibited Medications

Administration of the following medications is prohibited as specified below unless discussed and agreed with the Medical Monitor:

- Systemic or enteral therapy for pruritus in the 3 months prior to Screening. A subject may remain in the study if they require systemic or enteral therapy for pruritus after the initiation of investigational product administration.
- Administration of antibiotics within 1 month of Day 0 (unless subject is on a stable prophylaxis dose for at least 3 months prior to Day 0), except if administered for acute cholangitis whereby its use is prohibited within 3 months of Day 0.
- NOTE: Antibiotics are permitted as required during participation in the trial except amoxicillin/clavulanate (Augmentin) which has restrictions as detailed below.
- Prohibited from 6 months prior to Day 0 and throughout the LTSE phase of the trial unless as noted to discuss with Medical Monitor:
  - Fenofibrate or other fibrates
  - Potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
  - Amoxicillin/clavulanate (Augmentin) should not be used unless there are no other treatment options (this should be discussed with the Medical Monitor in advance of their use in this situation, where possible). Augmentin is also discouraged in the treatment of cholangitis but is not outright excluded (Section 7.4.2).

Subjects being administered the following medications at Day 0 may enter the trial provided they have been on a stable dose for ≥3 months prior to, and including, Day 0 and remain on a stable dose throughout the trial:

- Anti-TNF and anti-integrin antibodies
- Immunosuppressants (eg, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline)
- Corticosteroids
- Statins

8.3. Treatment Compliance

The Investigator should assess the subject's compliance with dosing of investigational product on an ongoing basis and at each contact and onsite visit; this should be confirmed by conducting drug accountability (ie, count of returned tablets) during subjects' on site visits.

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 drug 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 she/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. Continued trial eligibility should be assessed.

8.4. Randomization and Blinding

At Day 0, after review of Inclusion and Exclusion criteria, subjects will be allocated to 1 of 3 treatment groups in a 1:1:1 ratio based on a predefined randomization code (generated by the Sponsor or designee) using the IWRS, which will serve as the registration system for subjects at Screening, Day 0, and entry into the LTSE phase. The IWRS will serve as an investigational product inventory and management system and may be integrated with the trial 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 randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product dispensing information (eg. bottle number[s]) will be provided while maintaining the trial blind. The subjects, Investigator, and trial site staff will be blinded to the subject's treatment allocation during the subject's participation in the DB phase of the trial. The IWRS system will facilitate the unblinding of an individual subject at the time the subject completes the DB phase and enters the LTSE phase of the trial (ie, subjects' treatment allocations are unblinded one-by-one.

8.4.1. Stratification

In order to ensure that factors which could potentially affect treatment response are randomized in equal proportions to the different treatment groups, subjects will be stratified by the following:

- The presence or absence of concomitant UDCA use, where no more than 50% of subjects recruited will be administering UDCA as part of standard of care at Day 0
- Total bilirubin level, where no more than 25% of subjects recruited will have a total bilirubin >1.5x ULN and <2.5x ULN at Screening

8.4.2. Unblinding Procedures – Emergency Unblinding

For the DB phase of the trial, treatment assignment will be made available to the Investigator for emergency use only through the IWRS. 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 accidental unblinding or unblinding due to 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 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 DSMC (refer to Section 12.6.2) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 12.6.2 for further details regarding DSMC access to blinded and unblinded data. The DSMC will document, 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), details about any unblinded subject data reviews. Cases of premature unblinding (as noted above) will be reviewed by the DSMC.

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

8.5. Assignment of Site and Subject Numbers

8.5.1. Site Numbers

Each trial site selected to participate in this trial will be assigned a Site Number by the Sponsor. The Site Number will be used to identify the site and or Investigator within trial documents. This number will also be recorded in the CRF.

8.5.2. Subject Numbers

Subjects will be identified by a 6 digit number. The first 3 digits will represent the site number and the last 3 digits, the screening number. The first screening number used at any site will be 001 and as each new subject is screened, the subject will be assigned the next sequentially available number (eg, 001, 002, 003, etc).

8.6. Visit Procedures

8.6.1. Visit Windows

All trial visits during the DB period are relative to Day 0 (eg, if the Week 6 visit occurs 4 days late, the Week 12 visit should still be 12 weeks from Day 0). The Screening visit should occur ≤30 days (ie, Day -30 to Day -1) prior to the Day 0 visit. All visits during the DB treatment period should occur within ±1 week of the indicated time. The exception to this is the Week 2 visit, which should occur within ±3 days of the indicated time.

During the LTSE period, visits are relative to LTSE Day 1 (which is also the DB Week 24 visit) and all visits during this period should occur within ±2 weeks of the indicated time, except for the Week 2 Safety Contact which should occur within ±3 days and the Follow-Up visit, which should occur within ±1 week.

8.6.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, and risks of the trial to the subject and will provide him/her with a copy of the patient information sheet (PIS), containing the written information, and the informed consent form (ICF). The subject will be given sufficient time to consider the trial before deciding whether or not to participate, in line with local requirements where applicable. The subject will be informed that participation is voluntary and that her/his future medical treatment will not be compromised by participation in the trial and that she/he can withdraw from the trial at any time. The subject must be willing and able to

provide written informed consent before entering the trial. The Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the subject in the subject's medical notes/source worksheet. The subject will be provided with copies of their PIS and signed and dated ICF.

At selected trial sites, subjects will have the option to consent to participate in an additional PK and bile acid assessment.

As part of the consenting process, the Investigator or designee will describe the intention for and implications of providing blood samples for the analysis of RNA to each subject. Subjects who agree to provide these samples will be required to sign a separate ICF and will be provided with a copy of this, in addition to the overall study ICF. The samples will be stored for up to 1 year after the end of the study.

8.6.3. Screening Procedures (Within 30 Days of Day 0)

The Screening visit assessments must be performed within ≤30 days (ie, Day -30 to Day -1) prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria.

Subjects who do not meet all eligibility criteria during Screening may undergo repeat Screening assessments (one repeat only) at any time after 30 days from their initial date of consenting for the trial. Re-screened subjects will be allocated a new screening number.

The term "Baseline" within this protocol, unless otherwise specified, is intended to mean, "pretrial" or "pretreatment" (of investigational product). It refers to values obtained during the Screening, retests, or Day 0 visits, prior to the subject's first dose of investigational product. The statistical or calculated definition(s) of "Baseline" to be used in the analyses of the data may be different and will be further defined in the statistical analysis plan (SAP) for this trial.

Screening visit procedures are as follows:

- The subject is to review the PIS and sign the ICF. Written informed consent must be obtained from the subject before performing any trial related procedures, including Screening procedures. (Note: Collection of AEs commences from the point the subject signs the consent form.)
- Assign subject number.
- Collect medical history.
- Record prior (within 30 days of Screening) and current concomitant medications.
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination, including height and weight. See Section 11.2.2 for physical examination requirements.
- Record vital signs.
- Perform a standard 12-lead electrocardiogram (ECG).
- Perform hepatic ultrasound to assess bile duct patency.

- For subjects with UC: provide the diary and request subject completes this the day prior to the Day 0 visit, to reflect their symptoms since the Screening visit.
- For subjects with CD: provide the diary and request subject completes this for each of the 7 consecutive days prior to the Day 0 visit.
- Obtain blood samples for serum chemistry, hematology, and coagulation.

  Note:
  If a subject has an ALP value <2x ULN, a further sample may be taken during the Screening period (at least 14 days after the initial sample was taken), and provided the mean ALP is ≥2x ULN, the subject will have met inclusion criterion 4 (ALP at Screening ≥2x ULN)

  If a subject has a total bilirubin value >1.5x ULN, a further sample may be taken during the Screening period (at least 14 days after the initial sample was taken), and provided the mean total bilirubin is <2.5x ULN, the subject will have met inclusion criterion 5 (total bilirubin at Screening <2.5x ULN – in line with the bilirubin stratification factor: no more than 25% of subjects recruited will have a bilirubin >1.5x ULN and <2.5x ULN).
- Obtain urine sample for dipstick analysis
- Perform a urine-based beta human chorionic gonadotrophin (β-hCG) pregnancy test in females of childbearing potential. If the urine pregnancy test is positive, it should be repeated as a serum pregnancy test.
- The subject should be:
  - Provided with a fecal sampling kit and instructed to collect the sample within 2 days of their Day 0 visit, as described in the laboratory manual.
  - Instructed to fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all on site trial visits, but water is permitted.

8.6.4. Day 0 Procedures

- Verify inclusion and exclusion criteria for eligibility.
- Record current concomitant medications.
- Record vital signs.
- Perform transient elastography (TE) at sites where the Fibroscan® TE device is available.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy) using the data from the diary card provided at the Screening visit. See Appendix B for details.
- For subjects with CD: complete CDAI assessments using the data from the diary card provided at the Screening visit. See Appendix F for details.
- Administer pruritus visual analogue scale (VAS) subject questionnaire and 5-D Itch Questionnaire. See Appendix C for details.

- Assess and record AEs.
- Obtain blood samples for the following:
  - Serum chemistry, hematology, and coagulation
  - FGF-19
  - C-reactive protein (CRP)
  - Enhanced liver fibrosis (ELF) markers and other analytes
  - Plasma bile acids and 7α-hydroxy-4-cholesten-3-one (C4)
  - Apolipoprotein and nuclear magnetic resonance (NMR) lipoprotein panel
  - Genetics study (if subject has consented to provide a sample for RNA analysis)
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Obtain fecal sample for calprotectin and microbiome assessments (from subjects willing to provide a fecal sample).
- After verifying eligibility, randomize the subject via the IWRS system.
- Dispense the indicated investigational product.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- Reiterate dosing instructions and advise the subject:
  - All subjects are to administer the first dose of investigational product on Day 1 and administration of investigational product should occur at approximately the same time of day throughout the duration of the trial. Further details are included in Section 8.1.
  - NOT to take investigational product on the morning of the next trial visit, and
  - To bring the investigational product bottle(s) and
  - To fast overnight (at least 8 hours) prior to the next trial visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.

8.6.5. Week 2 Procedures

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).

- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch Questionnaire.
- Obtain blood samples for serum chemistry, hematology, and coagulation.
- 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 trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- Reiterate dosing instructions and advise the subject:
  - NOT to take investigational product on the morning of the next trial visit, and
  - To bring the investigational product bottle(s) and
  - To fast overnight (at least 8 hours) prior to the next trial visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.

8.6.6. Week 6 Procedures

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for serum chemistry, hematology, and coagulation.
- 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 trial

visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.

- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.
- The subject should be provided with a fecal sampling kit and instructed to collect the sample within 2 days of her/his Week 12 visit, as described in the laboratory manual.

8.6.7. Week 12 (Titration Visit) Procedures

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for the following:
  - Serum chemistry, hematology, and coagulation
  - FGF-19
  - CRP
  - ELF markers and other analytes
  - Plasma bile acids and C4
  - Apolipoprotein and NMR lipoprotein panel
- For sites and subjects participating in PK sampling: obtain samples for PK analysis (see Section 10.5 for sampling schedule). Subjects undergoing PK sampling should take the currently assigned dose (ie, lower dose); the titrated dose should be taken by the subject the following day.

- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Obtain fecal sample for calprotectin and microbiome assessments (from subjects willing to provide a fecal sample).
- 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 trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS and indicate if the subject will follow the titration schedule and dispense bottles of investigational product as indicated by IWRS.

  Note: The subject's dose will be titrated as follows, providing there are no limiting safety, or tolerability concerns in the opinion of the Investigator, while maintaining the trial blind: the 1.5 mg OCA treatment group will titrate to 3 mg, the 5 mg OCA treatment group will titrate to 10 mg OCA, and the placebo group will remain on placebo. DB treatment will continue for a further 12 weeks at that dose.

  Any subjects whose dose is not titrated, due to safety or tolerability concerns, will remain on their starting treatment (1.5 mg OCA, 5 mg OCA, or placebo) for the remainder of the DB phase to Week 24.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.

8.6.8. Week 14 Procedures

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.

- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for serum chemistry, hematology, and coagulation.
- 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 trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted.

8.6.9. Week 18 Procedures

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for serum chemistry, hematology, and coagulation.
- 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 trial

visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.

- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted.
- The subject should be provided with a fecal sampling kit and instructed to collect the sample within 2 days of their Week 24 visit, as described in the laboratory manual.

8.6.10. Week 24/LTSE Day 1 Procedures

- Assess and record AEs.
- Record current concomitant medications.
- Perform a physical examination, including weight.
- Record vital signs.
- Perform a standard 12-lead ECG.
- Perform TE at sites where the Fibroscan® TE device is available.
- Perform hepatic ultrasound to assess bile duct patency.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Subject to complete the Subject Research Questionnaire.
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - FGF-19
  - CRP
  - ELF markers and other analytes
  - Plasma bile acids and C4

  - Apolipoprotein and NMR lipoprotein panel
  - Genetics study (if subject has consented to provide a sample for RNA analysis)
- For sites participating in PK sampling: obtain samples for PK analysis (see Section 10.5 for sampling schedule).
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Obtain fecal sample for calprotectin and microbiome assessments (in subjects willing to provide a fecal sample).
- 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 trial visits, but water is permitted.
- Record the visit in the IWRS and indicate if the subject plans to participate in the LTSE.

For Subjects Participating in the LTSE:

- Re-confirm their consent to participate in the LTSE phase of the trial.
- Unblind the subject's treatment allocation in IWRS (as detailed in a separate trial document) and document the dose of OCA on which the subject will commence the LTSE.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Dispense indicated bottle(s) of investigational product.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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); and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at each visit after all assessments have been performed.

For Subjects NOT Participating in the LTSE:

- Remind the subject of the date of their Follow-Up visit.
- Perform a final investigational product accountability check verifying the amount of investigational product dispensed and returned.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).

8.6.11. Early Discontinuation and/or Early Termination Procedures: Double-Blind Phase

Subjects who terminate participation in the trial prior to the Week 24 visit should have an EOT visit as soon as possible following the decision to discontinue therapy. EOT visit procedures are as follows:

- Assess and record AEs.
- Record current concomitant medications.
- Perform a physical examination, including weight.
- Record vital signs.
- Perform a standard 12-lead ECG.
- Perform TE at sites where the Fibroscan® TE device is available.
- Perform hepatic ultrasound to assess bile duct patency.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Subject to complete the Subject Research Questionnaire.
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - FGF-19
  - CRP
  - ELF markers and other analytes
  - Plasma bile acids and C4
  - Apolipoprotein and NMR lipoprotein panel
  - Genetics study (if subject has consented to provide a sample for RNA analysis)
  - For sites participating in PK sampling: obtain samples for PK analysis (see Section 10.5 for sampling schedule)

- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Obtain fecal sample for calprotectin and microbiome assessments (in subjects willing to provide a fecal sample).
- Assess investigational product compliance and perform accountability; retrieve used bottles 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.
- Perform a final investigational product accountability check verifying the amount of investigational product dispensed and returned.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- Remind the subject of the date of their Follow-Up visit.
- Record the visit in IWRS.

8.6.12. Follow-Up Visit: Double-Blind Phase

Subjects who terminate participation in the trial prior to the Week 24 visit or complete the Week 24 visit but do not proceed to LTSE, should have a Follow-Up visit 4 weeks after their last dose of investigational product:

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for serum chemistry, hematology, and coagulation.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Record the visit in IWRS.

8.6.13. Long-Term Safety Extension Visits

LTSE visits will take place once every 3 months ±2 weeks.

If the Investigator is planning on up-titrating a subject during the LTSE, the subject needs to attend an additional study visit (Pre-Titration visit) as well as have a study contact.

Pre-Titration Visit

The Pre-Titration visit occurs approximately 1 week prior to the scheduled LTSE visit to assess serum chemistry (ie, ALP and bilirubin) and complete all other laboratory assessments.

Titration Visit

Following the Pre-Titration visit, the subject attends for the scheduled 3 monthly visit to determine her/his eligibility for titration. All procedures (except laboratory sample collection) for the scheduled trial visit occur as noted in the Schedule of Trial Procedures (Table 2). Subjects experiencing significant AEs (eg, severe pruritus) or other symptoms that are not tolerated, may not be eligible for titration. Under these circumstances, the Investigator should contact the Intercept Medical Monitor if he/she still plans to up-titrate the subject.

Contact

The Investigator or designee should contact the subject approximately 2 weeks after the Titration visit to assess for AEs. This contact will be recorded in the CRF. The Investigator may schedule an at-clinic Unscheduled/Safety visit at any time if clinically warranted.

If the Investigator is not planning on up-titrating a subject during an LTSE visit, the subject attends the scheduled 3 month visit without an additional visit or contact.

8.6.14. LTSE Day 1 (DB Week 24) Procedures

See Section 8.6.10 for the LTSE Day 1 (DB Week 24 visit) procedures.

8.6.15. LTSE Week 2 Procedures

The subject will be contacted by the study site staff 2 weeks after the start of the LTSE phase to assess safety.

8.6.16. LTSE Month 3, 9, 15, and 21 Procedures

The following procedures will occur at the Month 3, 9, 15, and 21 LTSE visits:

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for serum chemistry, hematology, and coagulation.

- Perform a urine based beta β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- 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 trial visits, but water is permitted.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS and dispense indicated bottles of investigational product.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted.
- **For the Month 9 and Month 21 visits only**:
  - The subject should be provided with a fecal sampling kit and instructed to collect the sample within 2 days of their next visit, as described in the laboratory manual.
- **For the Month 21 visits only**:
  - The subject should be advised that their last dose of investigational product is administered on the day prior to their Month 24 visit.

8.6.17. LTSE Month 6 Procedures

The following procedures will occur at the Month 6 LTSE visit:

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation

  - CRP
  - Plasma bile acids and C4
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- 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 trial visits, but water is permitted.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS and dispense indicated bottles of investigational product.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted.

8.6.18. LTSE Month 12 Procedures

The following procedures will occur at the Month 12 LTSE visit:

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- Perform TE at sites where the Fibroscan® TE device is available.
- Perform hepatic ultrasound to assess bile duct patency.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation

  - FGF-19
  - CRP
  - ELF markers and other analytes
  - Plasma bile acids and C4
  - Genetics study (if subject has consented to provide a sample for RNA analysis)
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Obtain fecal sample for calprotectin and microbiome assessments (in subjects willing to provide a fecal sample).
- 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 trial visits, but water is permitted.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS and dispense indicated bottles of investigational product.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted.

8.6.19. LTSE Month 18 Procedures

The following procedures will occur at the Month 18 LTSE visit:

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.

- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - CRP
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- 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 trial visits, but water is permitted.
- Assess investigational product compliance and perform accountability; retrieve used bottles and document returns.
- Record the visit in IWRS and dispense indicated bottles of investigational product.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- 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) and
  - To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted.

8.6.20. LTSE Month 24 Procedures

The following procedures will occur at the Month 24 LTSE visit:

- Assess and record AEs.
- Record current concomitant medications.
- Perform a physical examination, including weight.
- Record vital signs.
- Perform a standard 12-lead ECG.
- Perform TE at sites where the Fibroscan® TE device is available.
- Perform hepatic ultrasound to assess bile duct patency.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.

- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Subject to complete the Subject Research Questionnaire
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - FGF-19
  - CRP
  - ELF markers and other analytes
  - Plasma bile acids and C4
  - Genetics study (if subject has consented to provide a sample for RNA analysis)
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Obtain fecal sample for calprotectin and microbiome assessments (in subjects willing to provide a fecal sample).
- 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.
- Perform a final investigational product accountability check verifying the amount of investigational product dispensed and returned.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- Remind the subject of the date of their Follow-Up visit.
- Record the visit in IWRS.

8.6.21. Early Discontinuation and/or Early Termination Procedures: LTSE Phase

Subjects who terminate participation in the trial during the LTSE should have an EOT visit as soon as possible following the decision to discontinue therapy. EOT visit procedures are as follows:

- Assess and record AEs.
- Record current concomitant medications.
- Perform a physical examination, including weight.
- Record vital signs.
- Perform a standard 12-lead ECG.

- Perform TE at sites where the Fibroscan® TE device is available.
- Perform hepatic ultrasound to assess bile duct patency.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.
- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Subject to complete the Subject Research Questionnaire
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - FGF-19
  - CRP
  - ELF markers and other analytes
  - Plasma bile acids and C4
  - Genetics study (if subject has consented to provide a sample for RNA analysis)
- Obtain urine sample for dipstick urinalysis.
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Where possible, obtain fecal sample for calprotectin and microbiome assessments (in subjects willing to provide a fecal sample).
- Perform a final investigational product accountability check verifying the amount of investigational product dispensed and returned.
- Subjects with UC or CD: provide the appropriate diary card and request this is completed for the 7 consecutive days prior to their next scheduled visit (for subjects with CD) and the day prior to their next scheduled visit (for UC subjects).
- Remind the subject of the date of their Follow-Up visit.
- Record the visit in IWRS.

8.6.22. Follow-Up Visit: LTSE

All subjects who entered LTSE attend for a Follow-Up visit 4 weeks after their last dose of investigational product:

- Assess and record AEs.
- Record current concomitant medications.
- Record vital signs.
- For subjects with UC: obtain partial Mayo score (excluding endoscopy).
- For subjects with CD: complete CDAI assessments and assign CDAI score.

- Administer pruritus VAS subject questionnaire and 5-D Itch questionnaire.
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
- Perform a urine based β-hCG pregnancy test in females of childbearing potential. If the urine pregnancy test is positive it should be repeated as a serum pregnancy test.
- Record the visit in IWRS.

8.6.23. Unscheduled Safety Visit

The Investigator may schedule an Unscheduled/Safety visit at any time if clinically warranted or requested by the Medical Monitor. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. As appropriate, the Medical Monitor should be contacted.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

For the purpose of this protocol, the term "investigational product" describes both OCA and placebo tablets.

The investigational product used for this trial will be 1.5 mg and 5 mg OCA and matching placebo tablets. The 1.5 mg OCA tablet and matching placebo are white, round tablets with no markings. The 5 mg OCA tablet and matching placebo are white, round tablets debossed with "INT" on one side and "3547" on the other side. OCA tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

All investigational product will be provided as a tablet for oral administration and provided in high density polyethylene bottles with an induction seal and child resistant closures. The 1.5 mg OCA tablet and matching placebo are smaller tablets (approximately 6 mm diameter) and will be provided in 40 cc bottles. The 5 mg OCA and matching placebo (approximately 8 mm diameter) and will be provided in 85 cc bottles.

All investigational product will be manufactured according to Good Manufacturing Practice (GMP).

9.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to GMP standards by a designated qualified vendor. A designated vendor will also be responsible for the distribution of the investigational product to the Investigator and, where applicable, for providing the Qualified Person release of the investigational product.

Investigational product will be packaged and labeled as single bottles containing 100 OCA or placebo tablets and should be dispensed to the subject as received. For the DB phase of the clinical study, investigational product bottles will be blinded. Each bottle will be labeled with a

unique non-sequential bottle number. More than one bottle of investigational product may be dispensed to the subject at a visit to provide sufficient tablets for daily dosing until the next trial visit.

9.3. Investigational Product Storage

The investigational product should be stored in the containers in which it is received from the Sponsor's supplier, at 15°C to 25°C.

9.4. Investigational Product Administration

Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1). Investigational product administration should occur at approximately the same time of day throughout the duration of the trial. Subjects must be instructed to swallow the indicated number of tablets whole with water; they must not chew, divide, or crush the tablets.

9.4.1. Investigational Product Dispensation

On Day 0, after confirmation of subject eligibility, the Investigator or designee will dispense investigational product to the subject. Subjects will receive 2 bottles of investigational product on Day 0. Before leaving the clinic, trial site staff will ensure that the subject fully understands the dosing instructions.

At the 12 Week visit during the DB phase of the clinical study, subjects will receive 4 bottles of investigational product.

During the LTSE phase of the trial, subjects will receive 1 or 2 bottles of investigational product per visit depending on the dose of OCA they are receiving.

If necessary in exceptional circumstances, and only after approval by Intercept, investigational product may be delivered to subjects by courier, with proper precautions and documentation of shipping.

9.4.2. Missed Doses

Subjects who miss a dose of investigational product should be instructed to take it later the same day, as soon as they remember. Missed doses should not be taken on a subsequent day (ie, the subject should not take more than the prescribed daily dose, as directed).

9.4.3. Overdose

The maximum dose of OCA that has been given to humans is 500 mg as a single dose and 250 mg as a multiple dose. Reversible increases in aminotransferases were seen in most of the healthy volunteers who took 250 mg OCA. If overdose occurs in a subject enrolled in the trial, general medical supportive measures should be provided, including observation and follow-up (eg, serum chemistry) as appropriate. Due to the extensive enterohepatic recirculation of OCA it is likely that it will take several days before blood (and organ) concentrations of the drug will decrease. Treatment with cholestyramine (eg, Questran™), colesevelam (eg, Welcol™) and other BAS is recommended given that they should bind and eliminate the drug in feces. The Sponsor should be notified immediately in the event of a significant overdose.

9.5. Investigational Product Accountability and Disposal

A designated vendor will send investigational product to the trial 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 trial 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, missed doses, tablets/bottles returned at each visit, and final return or disposition (as directed by the Sponsor).

The trial 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 trial is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return to depot or destruction of the investigational product by the trial site.

10. ASSESSMENTS OF EFFICACY

10.1. Sample Collection

Blood samples for the assessment of efficacy will be collected at visits indicated in the Schedule of Trial Procedures (Table 1 and Table 2, Section 6.1). The complete list of planned assessments can be found in Appendix A.

Fasting (8 hours) blood samples are required for efficacy analyses. For consistency, subjects will be instructed to attend each of their at-site visits 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 onsite visits.

Fecal samples will be collected in a subset of subjects for the assessment of GI inflammation, at visits indicated in the Schedule of Trial Procedures.

Instructions concerning the number and type of samples, including the PK assessments, to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a trial-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.

10.2. Primary Efficacy Assessments

The primary efficacy assessment is serum ALP.

10.3. Secondary Assessments

Hepatic Biochemistry and Indices of Function

Hepatic biochemistry and indices of function will be assessed by measuring the following:

ALP, ALT, AST, GGT, bilirubin, albumin, and international normalized ratio (INR)

Hepatic and GI Inflammation, Hepatic Disease and Fibrosis

Hepatic and GI inflammation, hepatic disease, and fibrosis will be assessed by measuring the following:

Autotaxin and its metabolites, calprotectin, C-reactive protein (CRP), Cytokeratin-18 (CK-18), ELF markers, transient elastography (TE), Immunoglobulin A (IgA), IgG, Immunoglobulin M (IgM), Interleukin-6 (IL-6), Interleukin-12 (IL-12), Interleukin-23 (IL-23), transforming growth factor-beta (TGF-β), tumor necrosis factor-alpha (TNF-α).

The Enhanced Liver Fibrosis (ELF™) test is a blood test that measures hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and a tissue inhibitor of metalloproteinase 1 (TIMP-1), as a measure of hepatic fibrosis.

Transient Elastography (TE) is an assessment of hepatic fibrosis using a Fibroscan® TE device (Echosens, Paris, France) that measures hepatic stiffness. It is a validated and non-invasive measure and will be performed at trial sites that have the equipment. Trial sites must have staff trained in the use and data interpretation of the device.

GI inflammation will be assessed by measuring fecal calprotectin in subjects who provide fecal samples.

FXR Activity

FXR activity will be assessed by measuring fibroblast growth factor-19 (FGF-19) concentrations.

Disease-Specific Symptoms

Disease-specific symptoms of IBD and pruritus will be assessed using the partial Mayo score (only for subjects with UC), CDAI (only for subjects with CD) and as a Pruritus VAS and 5-D itch questionnaire, respectively.

IBD Symptoms

- Partial Mayo Score

The partial Mayo score will be performed by the Investigator at specified visits to assess symptoms associated with IBD (Rutgeerts 2005). The full Mayo scoring system includes questions related to stool frequency and rectal bleeding, endoscopic findings, and the physician's global assessment. The partial score does not include an endoscopy and will be used in this trial. Details of the partial Mayo Ulcerative Colitis Score are shown in Appendix B.

- CDAI

The CDAI will be performed by the Investigator at specified visits to assess symptoms associated with CD (Best 1976) and will be based on the subject's recount of their symptoms in addition to hematocrit and body weight measurements. Details of the CDAI are shown in Appendix F.

To assist sites with recording and calculating the partial Mayo score and the CDAI, subjects with UC will be asked to complete a diary the day prior to the next scheduled visit, recording details since their last visit; and subjects with CD should complete the diary in the 7 days prior to their next clinic visit. The PI will transcribe relevant information into the subject's medical records for SDV and retain the diary cards. Pertinent aspects of these data will be recorded in the CRF. Data from the Screening period diary card will be recorded at Day 0.

Pruritus

In addition to the assessment of pruritus as an AE with mild, moderate and severe categories, pruritus will be specifically assessed by patient questionnaires:

- Pruritus VAS

Subjects will be asked to complete the Pruritus VAS to assess any experiences of pruritus during the trial; they will be asked to initial and date to document confirmation of their responses, and the questionnaires should be filed in the subject's trial records. Details of the Pruritus VAS are shown in Appendix C.

- 5-D Itch 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).

10.4. Additional Exploratory Assessments

Gut Microbiome Genetic Profile

The gut microbiome will be assessed from fecal samples provided by subjects who agreed to provide fecal samples.

Genetics Study

RNA expression resulting from treatment with OCA will be assessed at indicated timepoints during the trial. Subjects will be permitted to decline to provide a blood sample for the genetics study, without affecting their involvement in the trial. 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.

Exploratory Analytes

Blood samples for future analysis related to the effects of OCA or FXR activation will be collected at specified timepoints during the study and may be assayed on an exploratory research basis. The samples will be stored for up to 2 years after the end of the study.

Subject Research Questionnaire

A Subject Research Questionnaire will be administered upon completing participation in the DB phase – either at the DB Week 24 visit or, if the subject terminates early during the DB phase, or at the EOT visit. This simple questionnaire requests feedback about the subject's perception of the trial and asks subjects if they felt that their participation in the trial was worthwhile and whether they would recommend a similar trial to a family member. The Subject Research Questionnaire is included in Appendix E.

10.5. Pharmacokinetics and Bile Acid Assessments

At selected investigational sites, subjects will have the option to consent to participate in an additional PK and bile acid assessment. This is optional and subjects may decline to participate without affecting their involvement in the rest of the trial.

OCA and its conjugates will be assessed at indicated visits and times (see Table 1 and Table 2). In addition, total bile acids, UDCA, OCA, CDCA, LCA, cholic acid, deoxycholic acid (conjugated and unconjugated forms) and C4 will also be analyzed.

Following collection of the fasted laboratory samples (8 hour overnight fast) at Week 12 and Week 24 (as noted in Table 1), subjects who are participating in the PK/bile acid assessment will each receive a single dose of their allocated investigational product with approximately 240 mL of water. At Week 12, subjects will receive their dose assigned prior to titration (ie, the lower dose of investigational product). 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. The trial-specific laboratory manual will include details of the volume of blood required to be drawn during each sampling timepoint as well as other logistical details and sample handling requirements.

Subjects should not drink additional water for 1 hour after taking the dose of investigational product. After approximately 1 hour postdose, subjects will be fed a meal replacement drink.

As a secondary efficacy analysis, an exposure response analysis of total plasma OCA (OCA and its conjugates) to biomarkers, such as change in ALP and change in bile acids, will be performed to help identify optimal doses for this patient population.

11. ASSESSMENT OF SAFETY

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

11.1. Adverse Events and Serious Adverse Events

11.1.1. Definitions

11.1.1.1. Adverse Event

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

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the trial; (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.

11.1.1.2. Serious Adverse Event

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

- Death;
- Is immediately life threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Results in a congenital abnormality or birth defect;
- Is an important medical event that may jeopardize the 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.

11.1.1.3. Treatment Emergent Adverse Event

A treatment emergent adverse event (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.

11.1.2. Relationship to Investigational Product

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

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

Table 7: Relationship of AEs 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 drug; 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.

11.1.3. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity). A severity category of mild, moderate, or severe, as defined in Table 8 must be entered on the AE 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 8: Severity of AEs

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.

11.1.3.1. Severity of Pruritus (as an AE)

Pruritus was the most common AE seen in the Phase 2 and Phase 3 PBC trials and thus may occur in this trial. Subjects experiencing, or who have experienced within ≤3 months of

Screening, pruritus requiring systemic or enteral treatment are excluded from participating in this trial.

To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used both for AE reporting and during pretreatment assessment. As pruritus is a subjective symptom, clinical judgment should be used to determine its severity and management. Subjects who experience a treatment emergent AE of severe pruritus should not be titrated to a higher dose.

Table 9: Severity of Pruritus

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

In the phase 2 PBC trials, Investigators tried a number of different approaches to help relieve pruritus symptoms. Severe pruritus typically appears to occur shortly (ie, within the first 2 weeks after starting therapy). In the 747-202 trial, about 80% of the patients who were started on BAS or other drugs or interventions during the trial completed the trial as planned. In the Phase 3 trial, similar approaches were employed in addition to evaluation of lower doses: 27% of subjects in the 10 mg group added a BAS compared to 20% of subjects in the titration arm and 11% of placebo subjects. Consistent with the use of lower doses and pruritus mitigation strategies withdrawals due to pruritus were minimized (1 subject in the titration arm and 7 in the 10 mg OCA arm withdrew due to pruritus compared to none in the placebo arm).

Since pruritus is such a subjective symptom (and the most common symptom in PBC patients), clinical judgment needs to be applied to the management of each subject. However, the following recommendations are made for the management of subjects experiencing significant pruritus in this PSC trial:

- Prescribe BAS, eg, cholestyramine, colestipol, colestimide, or colesevelam. The greatest experience to date has been with cholestyramine. Theoretically, colesevelam may be more palatable (tablet) and more effective. Patients taking BAS should be instructed to stagger their dosing of investigational product and UDCA ensuring at least 4 hours between doses of the BAS and investigational product (and UDCA).

- Dose frequency modification: Less frequent dosing of investigational product (eg, on alternate days) may be tried, after which subjects may return to their original daily dose, if and as tolerated.
- Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). For subjects with severe pruritus, instruct the subject to stop taking investigational product until the pruritus subsides to an acceptable level at which time it should be restarted (likely, on a modified, alternate day dosing schedule). Details of drug holidays and/or nondaily dosing regimens should be recorded in the CRF. Such cases should be discussed with the Medical Monitor.
- Other therapies may be tried as deemed clinically appropriate.

11.1.4. Reporting of Adverse Events and Serious Adverse Events

11.1.4.1. 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 trial participation of the trial.

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.

11.1.4.2. 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. SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by:

- E-mail to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: +1 800 497 8521
- Telephone: + 1 844 250 6398

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 trial within the time frames required by each regulatory agency. An SAE assessed with possible, probable, or definite causal relationship to the investigational product and unexpected according to the IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR). The Investigator must report SUSARs using the SAE reporting method described above.

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 Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, in compliance with the local country requirements. For the European Union, the Sponsor will notify the regulatory agencies and report SUSARs via the Eudra Vigilance database within 7 calendar days of a SUSAR involving death or a life-threatening SUSAR, and all other SUSARs within 15 calendar days. Documentation of the submissions to IRBs/IECs and health authorities (as applicable) must be retained in the appropriate trial file(s). As instructed by the Sponsor, Safety Reports/Expedited Safety Reports should be retained in the appropriate Investigator site trial files, or with the IB.

11.1.5. Anticipated Serious Adverse Events Associated with PSC

There are a number of events which are commonly associated with PSC and for the Sponsor's regulatory reporting purposes, these events are considered to be 'Expected' in this patient population and are listed in the IB.

The Investigator remains responsible for reporting to the Sponsor all SAEs including the events identified here:

- GI and hepatic malignancies including CCA, pancreatic cancer, colorectal cancer
- Ascites
- Cholecystitis
- Cholangitis (including bacterial cholangitis)
- Pancreatitis
- IBD and IBD flare (including UC and CD)
- Bile duct strictures (dominant or otherwise)
- Steatorrhea

- Vitamin deficiency
- Osteoporosis/osteopenia
- Fractures
- Variceal bleeding
- Cirrhosis
- Worsening PSC
- Any of the above that result in Death

11.1.6. Additional Investigator Responsibilities for SAEs

The safety data recorded in the CRF represent the official record of all AEs and SAEs reported in the trial. 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 Sponsor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for 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.

11.1.7. Notification of Post-Trial 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 trial, the Sponsor 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 trial, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 11.1.4.2.

11.1.8. Follow-Up of AEs and SAEs

All AEs must be followed during the course of the trial 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.

11.1.9. Pregnancy and Follow-Up

Pregnancies are not considered SAEs in and of themselves; however if a female trial participant becomes pregnant while she is enrolled in the clinical trial investigational product must be stopped immediately. The Sponsor must be notified within 24 hours of the Investigator's awareness 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**.

The subject must be followed by the Investigator through pregnancy outcome. The Investigator should notify the Sponsor of the outcome of the pregnancy by completing the Pregnancy Outcome Form and faxing or emailing to the Sponsor. The mother (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor.

The Investigator must contact the Intercept Medical Monitor and discuss, in advance, any subject whose pregnancy is early terminated and would like to continue to participate in the trial. A minimum requirement for allowing the subject to restart dosing is documentation of a negative serum β-hCG test. However, this is not in and of itself a guarantee for being allowed to continue in the study.

11.2. Other Safety Parameters

11.2.1. Medical History/Demographics

A complete medical history will be obtained from the subject at screening. Demographic characteristics (age, gender, race, ethnicity, etc) will be recorded, as will any historical or on study data on colonoscopies (mucosal and histological) within the last 3 years and prior and on study liver biopsies, hepatic imaging, etc. Reports should be available in source data.

11.2.2. Physical Examination

To assess the Subject for clinical findings, the Investigator or designee will perform a physical examination at the time points specified in the Schedule of Trial Procedures (Table 1 and Table 2). If clinically significant abnormalities are observed before administration of the first dose of investigational product on Day 1, they should be reported as adverse events. If clinically significant abnormalities are observed after the first administration of investigational product on Day 1, the Investigator should assess and decide if they are new adverse events and report them accordingly. The physical examination should include the following at a minimum:

- General appearance
- Height (Screening visit only)
- Weight
- Skin

- Head, eyes, ears, nose and throat (HEENT)
- Neck
- Lymph nodes
- Chest/Respiratory system
- Cardiovascular system
- Abdominal region
- Extremities
- Musculoskeletal system
- Mental status
- Neurological system.

11.2.3. Vital Signs

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

11.2.4. Electrocardiogram

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

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 ID number, date and time.

11.2.5. Laboratory Assessments

All laboratory tests will be analyzed by a Central Laboratory (except urine or serum pregnancy tests). Blood and urine samples will be collected and analyzed or tested, according to the SOP of the testing facility and all samples will be collected while the subject is fasting. Full instructions concerning the number, volume, and type of samples to be collected at each visit will be detailed in the trial-specific laboratory manual. The manual will also include details of sample collection methods, labelling, and shipping information.

Fasting (8 hours) blood samples are required for lipid, glucose (serum chemistry), and bile acid analyses. For consistency, subjects will be instructed to attend each of their onsite 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 whether 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, this should be documented accordingly in the source and CRF and remind the subject that fasting is required prior to all trial visits.

- Hematology and Coagulation (hemoglobin, hematocrit, white blood cell [WBC] count with differential, platelets, red blood cell [RBC] count, INR, prothrombin time, partial thromboplastin time)
- Serum chemistry including albumin, blood urea nitrogen (BUN), creatinine, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, total bilirubin, AST), ALT, ALP, GGT, electrolytes [calcium, chloride, potassium, sodium, magnesium], glucose, total protein, and blood lipids (total cholesterol, low density lipoprotein [LDL], HDL and very low density lipoprotein (VLDL) fractions and triglycerides [TG])
- Apolipoprotein and NMR lipoprotein panel: ApoA1, ApoB, ApoE, HDL, LDL, triglycerides, VLDL. HDL, LDL, and VLDL cholesterol concentrations, particle numbers and sizes will be assessed.
- IgG4 (Screening visit only)
- Urine dipstick (pH, specific gravity, protein, glucose, ketones, bilirubin, blood)

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 test-article related AE, is identified; or until further follow-up is deemed medically unnecessary.

Urine based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. Additionally, in accordance with local country or site requirements, additional urine pregnancy tests may be performed. 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 11.1.9 until pregnancy outcome.

12. STATISTICS

12.1. Analysis Populations

The following analysis populations will be used:

Intent-to-Treat (ITT) Population

All randomized subjects who receive any amount of investigational product will be included in the ITT population. Treatment assignment will be based on the randomized treatment. The ITT population will be used for the analysis of all efficacy data.

Week 12 Completer Population

Completer population will include all ITT subjects who complete the DB Week 12 ALP assessment. Treatment assignment will be based on the randomized treatment.

Week 24 Completer Population

Completer population will include all ITT subjects who complete the DB Week 24 ALP assessment. Treatment assignment will be based on the randomized treatment.

Safety Population

The Safety population will include all subjects who receive any amount of investigational product. Treatment assignment will be based on the treatment actually received. The Safety population will be used for the analysis of all safety data.

12.2. Determination of Sample Size

A sample size of 25 subjects per treatment group, a total of 75 subjects, will provide at least 90% power to detect a treatment difference for change in ALP assuming 20% dropout and the mean absolute changes in ALP for OCA and placebo treatment groups are approximately -20% and -5%, respectively, with a pooled standard deviation of 16, based on a 2-sided independent 2-group t-test at an alpha level of 0.05.

12.3. Efficacy Analysis

One of the primary objectives of this proof of concept trial is to evaluate the efficacy of OCA in subjects with PSC. The primary population for efficacy analyses is the ITT population. Sensitivity analyses will be conducted using the Completer population.

12.3.1. Primary Efficacy Analysis

The primary efficacy endpoint is the Week 24 change from Baseline in ALP. The primary efficacy analysis will compare the Week 24 change from Baseline in ALP between OCA 10 mg treatment group and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata, and Baseline as a covariate.

12.3.2. Secondary Efficacy Analysis

Secondary efficacy analyses of hepatic biochemistry and function parameters (eg, ALT, AST, and GGT) will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment. Hepatic biochemistry and function parameters will be analyzed using the same ANCOVA model as specified for the primary efficacy analysis.

A hierarchical approach will be used for multiplicity adjustments. If the primary efficacy analysis is statistically significant ($p < 0.05$), the following order will be used in the testing procedure to compare the change from Baseline in ALP between OCA and placebo:

- Week 12: OCA 5 mg treatment group (randomized to 5 mg for the initial 12 weeks followed by 10 mg for the latter 12 weeks) vs. placebo
- Week 24: OCA 3 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo
- Week 12: OCA 1.5 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo

If at any step a comparison above is not statistically significant, then all subsequent comparisons will be exploratory rather than confirmatory.

In addition, secondary efficacy analyses of ALP response rates, defined as ALP to <1.5x ULN, will compare OCA treatment groups and placebo at Week 12 and Week 24 using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

Hepatic stiffness measurements (based on TE) will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The ELF score and its components (HA, P3NP, T1MP-1) and the other markers of fibrosis and/or inflammation will be summarized based on available data by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will be analyzed using the same ANCOVA model as specified for the primary efficacy analysis.

Subgroup analyses will be evaluated as deemed appropriate, including but not limited to, those subjects who start antibiotics after first dose of investigational product.

Full details regarding the planned analyses, methods, and outputs for the trial will be included in the SAP.

12.4. Pharmacokinetics

PK parameters will be determined for OCA, glyco-OCA, tauro-OCA, and total OCA (OCA plus conjugates). PK parameters, including the following, will be calculated using non-compartmental methods where appropriate:

- C_{max}: maximum concentration (observed)
- t_{max}: time to C_{max}
- AUC_t: area under the concentration-time curve from time 0 to the last sampling time with measurable analyte concentration, calculated by the linear trapezoidal method

An exposure-response assessment will be made comparing endpoints such as ALP and bile acids (eg, change in ALP relative to baseline) to the average exposure of total OCA (eg, AUC or C_{ss} [steady-state concentration]) to help define an appropriate dose of OCA in this patient population.

Full details regarding the planned analyses, methods, and outputs for the trial will be detailed in the SAP.

12.5. Safety Analysis

12.5.1. Adverse Events

A treatment emergent AE (TEAE) is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of investigational product. AEs occurring between the signing of informed consent but prior to first dose of investigational product are considered pretreatment AEs. Treatment-emergent AEs will be summarized by treatment, system organ class, and preferred term defined using the Medical Dictionary of Regulatory Activities (MedDRA). The number of events, the number of subjects, and the percent of subjects who experienced at least one TEAE will be presented for each system organ class and for each preferred term by treatment group. TEAEs that lead to early withdrawals, serious TEAEs, and TEAEs by severity and relationship will be summarized in the same manner. Additional details will be provided in the SAP.

12.5.2. Clinical Laboratory Evaluations

Planned laboratory assessments are listed in Appendix A. All hematology, clinical chemistry, urinalysis, and fecal sampling results will be listed by treatment, subject, and visit, including scheduled and unscheduled/repeat measurements. Laboratory assessments that are outside of normal ranges will be flagged. Baseline values, the values at each visit, and changes from Baseline values will be summarized for each of the quantitative laboratory assessments by treatment group. Baseline is defined as the mean of all available evaluations prior to treatment (except for lipoprotein assessments where Baseline will be the fasted Day 0 assessment).

12.5.3. Additional Safety Analysis

Additional safety assessments include vital signs and ECGs. Vital signs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized. ECGs will be summarized by treatment group using frequency at each visit. The shift from baseline will also be summarized. Baseline is defined as the mean of all available evaluations prior to treatment.

12.6. Interim Analyses and Data Monitoring

12.6.1. Interim Analysis

An unblinded interim analysis will be conducted after approximately 50% of subjects have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint, the change from Baseline in ALP, between OCA treatment groups (1.5 mg and 5 mg) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. No adjustments to the alpha level will be made.

In addition, once all subjects have completed the DB phase of the study, the DB database will be locked, unblinded, and full analyses will be performed. The specific details of both the interim and end of double-blind analyses will be documented in the SAP.

12.6.2. Data and Safety Monitoring Committee

An independent DSMC will review safety data from this trial, as well as other ongoing OCA trials at approximately quarterly intervals, but at least every 6 months. The DSMC includes internationally recognized hepatologists, pharmaceutical physicians and statistician(s). 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 will 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 trial and will not otherwise consult for the Sponsor.

SAE information will be provided to the DSMC on an ongoing basis as SAEs occur. Adhoc (closed) DSMC meetings for review of unblinded data from subjects who experience SAEs, as

requested by the DSMC, will be arranged. 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 trial.

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 trial. The DSMC will prepare written minutes of both its open and closed sessions for each trial. 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 patient 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, MedDRA coded AEs, and AEs leading to early withdrawal of study drug. 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. At a minimum, the occurrence of 2 life threatening SAEs or an SAE resulting in death will trigger an unscheduled and unblinded review of the data by the DSMC.

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 trial. The Investigators will inform the subjects of such actions and the protocol, PIS and consent will be revised, as appropriate.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Trial Monitoring

Trial 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 trial, 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 trial to be closely followed by the Medical Monitor.

13.2. Investigator Audits and Inspections

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

14. 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 trial at the trial 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 trial data. Investigators' meetings and/or onsite trial initiations will be performed to prepare Investigators and other trial site personnel for appropriate collection of trial data.

To ensure compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

The final trial protocol, including the final version of the PIS and ICF 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 Intercept before he or she can enroll any subject into the trial. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to trial 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 substantial amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to trial participants. In addition, the IRB/ IEC must approve all advertising used to recruit subjects for the trial. The protocol must be reapproved by the IRB/ IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any SARs any other trial 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, as a minimum annually, and after the trial is complete.

15.2. Ethical Conduct of the Trial

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and are consistent with ICH/GCP, applicable regulatory requirements.

15.3. 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 trial. Subjects must also be notified that they are free to discontinue from the trial 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 trial procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

15.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the trial 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 trial 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 subjects' 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 trial 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 PIS will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may require direct access to parts of the hospital or trial site records relevant to the trial, including subject's medical history.

16. 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 trial. If the Investigator is not present in the trial site during the assessment, he or she will leave instructions for the trial 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.

16.1. AE Reporting

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

16.2. 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 trial 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.

16.3. Regulatory Documentation

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

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

16.4. Ethics Review

Please see Section 15.1 for the Investigator's responsibilities regarding ethics review.

16.5. Archiving and Record Retention

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

All Sponsor-specific essential documents relating to the trial, including the ISF itself, source documents and subject medical files (retained per country specific regulations), completed trial subject log, and confidential subject identification list will be retained by the Investigator for

until 2 years after the approval of a marketing application 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 trial site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

17. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical trials that it sponsors consistent with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 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 trial (http://www.icmje.org/ethical_1author.html, accessed May 22, 2013). 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 trial data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical trials that are appropriate for this trial. Key issues include the following:

- Clinical Trial Registries (eg, clinicaltrials.gov): A description of the trial and relevant design elements (eg, basic design, objectives and endpoints, sample size, trial 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 trial databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and the 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 trial. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the

costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.

- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting trial 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 trial and is designed to be published with complete data from all the trial sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are 'extracted' from a multicenter trial and that the trial was not intended, or statistically powered, for data presentation by a single trial site.
- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this trial 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 nonclinical studies or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent trial 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.

18. LIST OF REFERENCES

Al Mamari S, Djordjevic J, Halliday JS, et al. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. J Hepatol. 2013 Feb;58(2):329-34.

Albanis E, Alvarez CE, Pruzanski M, et al. INT-747, a novel FXR activator, reverses hepatic fibrosis and cirrhosis in thiocetamideinduced liver injury in rats. Hepatology. 2005;42(Supplement 1):Abstract 1040.

Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol. 2002 Mar;36(3):321-7.

Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976 Mar; 70 (3): 439-444.

Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006 Jun;3(6):318-28.

CEREP. In Vitro pharmacology:High-throughput profile - Study of INT-747. 2008 June 7, 2008;Study #14862.

Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010 Feb;51(2):660-78.

Chapman R. Primary sclerosing cholangitis. Autoimmune Liver Disease. 2011; 39(10):558-591.

Cipriani S, Mencarelli A, Chini MG, et al. The bile acid receptor GPBAR-1 (TGR5) modulates integrity of intestinal barrier and immune response to experimental colitis. PLoS One. 2011;6(10):e25637.

EASL. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. Journal of Hepatology. 2009;51:237-67.

Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology. 2013 Sep;145(3):521-36.

Elman S, Hynan L, Gabriel V, et al. The 5-D itch scale: a new measure of pruritus. British Journal of Dermatology. 2010 Dec; 162: 587-593

Fevery J, Verslype C, Lai G, et al. Incidence, diagnosis, and therapy of cholangiocarcinoma in patients with primary sclerosing cholangitis. Dig Dis Sci. 2007 Nov;52(11):3123-35.

Gadaleta RM, van Erpecum KJ, Oldenburg B, et al. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. Gut. 2011 Apr;60(4):463-72.

Hirschfield GM, Karlsen TH, Lindor KD, et al. Primary sclerosing cholangitis. Lancet. 2013 Nov 9;382(9904):1587-99.

Lazaridis KN, Gores GJ. Primary sclerosing cholangitis and cholangiocarcinoma. Semin Liver Dis. 2006 Feb;26(1):42-51.

Lee YM, Kim DJ. Primary Sclerosing Cholangitis. New England Journal of Medicine. 1995;332:924-33.

Lee YM, Kaplan M, and the Practice Guideline Committee of the ACG. Management of Primary Sclerosing Cholangitis. AJG 2002 Mar; 97(3):528-534.

Lefebvre P, Cariou B, Lien F, et al. Role of bile acids and bile acid receptors in metabolic regulation. Physiol Rev. 2009 Jan;89(1):147-91.

Levy C, Lindor KD. Primary sclerosing cholangitis: epidemiology, natural history, and prognosis. Semin Liver Dis. 2006 Feb;26(1):22-30.

Li YT, Swales KE, Thomas GJ, et al. Farnesoid x receptor ligands inhibit vascular smooth muscle cell inflammation and migration. Arterioscler Thromb Vasc Biol. 2007 Dec;27(12):2606-11.

Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. N Engl J Med. 1997 Mar 6;336(10):691-5.

Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009 Sep;50(3):808-14.

Lindstrom L, Hultcrantz R, Boberg KM, et al. Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2013 Jul;11(7):841-6.

Makishima M, Okamoto AY, Repa JJ, et al. Identification of a nuclear receptor for bile acids. Science. 1999 May 21;284(5418):1362-5.

Mookerjee RP, Mehta G, Balasubramaniyan V, et al, Hepatic dimethylarginine-dimethylaminohydrolase1 is reduced in cirrhosis and is a target for therapy in portal hypertension. J Hepatol. 2015 Feb; 62(2):325-331.

Olsson R, Boberg KM, de Muckadell OS, et al. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. Gastroenterology. 2005 Nov;129(5):1464-72.

Pellicciari R, Fiorucci S, Camaioni E, et al. 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity. J Med Chem. 2002 Aug 15;45(17):3569-72.

Pols TW, Noriega LG, Nomura M,: The bile acid membrane receptor TGR5 as an emerging target in metabolism and inflammation. J Hepatol. 2011;54:1263-1272.

Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.

Talwalkar JA, Chapman RW. The resurgence of serum alkaline phosphatase as a surrogate biomarker for prognosis in primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2013 Jul;11(7):847-9.

Wang H, Chen J, Hollister K, et al. Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol Cell. 1999 May;3(5):543-53.

Wang YD, Chen WD, Wang M, et al. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. Hepatology. 2008 Nov;48(5):1632-43.

Worthington J, Chapman R. Primary sclerosing cholangitis. Orphanet J Rare Dis. 2006;1:41.

APPENDIX A. LIST OF PLANNED LABORATORY ANALYTES

Serum Chemistry

alanine transaminase (ALT; SGPT)

albumin

alkaline phosphatase (ALP)

aspartate aminotransferase (AST; SGOT)

bicarbonate

bilirubin: total, unconjugated (indirect) & conjugated (direct)

blood urea nitrogen (BUN)

calcium

chloride

creatinine

free fatty acids

gamma-glutamyl transpeptidase (GGT)

glucose

HDL

LDL

magnesium

phosphorus

potassium

sodium

thyroid hormones (T3, T4, TSH)

total cholesterol

total protein

triglycerides

vitamin D

VLDL

Apolipoprotein and NMR Lipoprotein Analysis

ApoA1

ApoB

ApoE

HDL

LDL

triglycerides

VLDL

HDL, LDL, and VLDL cholesterol concentrations, particle numbers and sizes will be assessed.

Hematology

hematocrit

hemoglobin

platelets

RBC count (incl. MCV, HBE [MCH], MCHC)

WBC with differential

neutrophils*

lymphocytes*

monocytes*

eosinophils*

basophils*

Coagulation Parameters

prothrombin time (PT and INR)

partial thromboblastin time (PTT)

Biomarkers of Inflammation

autotaxin & its metabolites

CRP

IgA

IgG

IgG4

IgM

IL-6

IL-12

IL-23

TGF-β

TNF-α

Biomarkers of Fibrosis

Enhanced Liver Fibrosis (ELF) markers: Hyaluronic acid, P3NP, TIMP-1

CK-18

FXR Activity

FGF-19

Bile Acids (conjugated & unconjugated forms)

C4

CDCA

Cholic acid

Deoxycholic acid

Lithocholic acid

OCA

Total bile acids

UDCA

Genetics Test

RNA

Urine Dipstick

bilirubin

blood

glucose

ketones

pH

protein

specific gravity

Urine Pregnancy

Urine β-hCG pregnancy test in females of childbearing potential. If the urinary test is positive it should be repeated as a serum pregnancy test.

Fecal Samples

calprotectin

gut microbiome (fecal bacterial genome)

* Further evaluation if appropriate

Note: The above list is not all inclusive and some tests may not be performed if not required.

APPENDIX B. PARTIAL MAYO SCORING SYSTEM FOR ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY

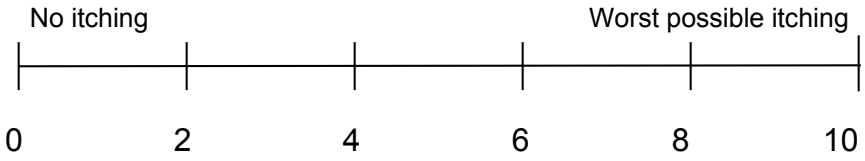
Partial Mayo Scoring System for Assessment of Ulcerative Colitis Activity (The Partial Mayo Score ranges from 0-9, with higher scores indicating more severe disease)
Stool Frequency (Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency) 0 = Normal no. of stools for this patient 1 = 1 to 2 stools more than normal 2 = 3 to 4 stools more than normal 3 = 5 or more stools more than normal Subscore, 0 to 3
Rectal Bleeding (The daily bleeding score represents the most severe bleeding of the day) 0 = No blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes Subscore, 0 to 3
Physician's Global Assessment (This assessment acknowledges the two other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status) 0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease Subscore, 0 to 3

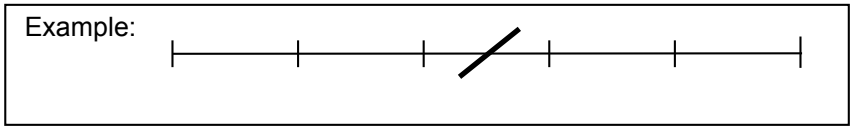
APPENDIX C. PRURITUS VISUAL ANALOGUE SCALE

Visual Analog Scale

Severity: Draw a line anywhere on the scale that best represents the severity of your itching

(See example below)





Note: Size of actual VAS is 10cm.

APPENDIX D. 5-D ITCH SCALE

5-D Pruritus Scale

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX E. SUBJECT RESEARCH QUESTIONNAIRE

Subject Research Questionnaire

We are very grateful to you for participating in this clinical study and hope that you found it worthwhile.

We ask that you spend a few minutes to complete the following questionnaire. We are interested in your views about this study and any comments that you may have.

Your identity will remain entirely confidential. Thank you!

Did you feel that participating in this clinical study was worthwhile? (1 – Disagree strongly - 5 – Agree strongly)	☐1 ☐2 ☐3 ☐4 ☐5 Comment:
Would you recommend participation in a clinical study to a relative or a close friend, with the same condition? (1 – Disagree strongly - 5 – Agree strongly)	☐1 ☐2 ☐3 ☐4 ☐5 Comment:
What were some of the features of the study that you liked (tick all that apply)?	☐ Better medical care / attention ☐ Helping others with my disease ☐ Better understanding of my disease ☐ Friendly environment with other patients ☐ Study offered good change from usual routine ☐ Other, please specify: Comment:
What were some of the features of the study that you disliked (tick all that apply)?	☐ Study was overly invasive ☐ Expectations of study were not met ☐ Study was overly disruptive to usual routine ☐ Medical care was less than I expected ☐ Interaction with medical staff was less than I expected ☐ Other, please specify: Comment:

Thank you very much for your participation.

APPENDIX F. CROHN'S DISEASE ACTIVITY INDEX

(CDAI: adapted from Best 1976)

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for seven days	x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days	x 5
General wellbeing, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	x 7
Presence of complications*	x 20
Taking Lomotil or opiates for diarrhea	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10
Hematocrit of <0.47 in men and <0.42 in women	x 6
Percentage deviation from standard weight	x 1

*One point each is added for each set of complications:

- the presence of joint pains (arthralgia) or frank arthritis
- inflammation of the iris or uveitis
- presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- anal fissures, fistulae or abscesses
- other fistulae
- fever during the previous week

APPENDIX G. PROTOCOL VERSION 2 – SUMMARY OF CHANGES

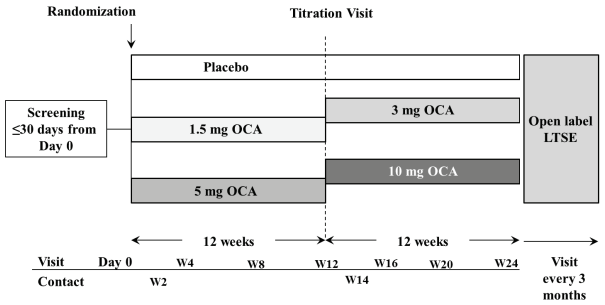
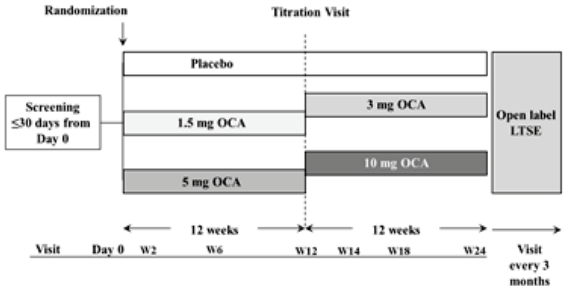
1. **Background**
   Protocol 747-207 has been prepared as a Phase 2 trial to evaluate the potential clinical benefit of OCA in PSC.

   The original protocol dated 06 June 2014 was submitted to the US FDA on 29 July 2014. Comments were received by Intercept Pharmaceuticals on 21 August 2012. The original protocol was not submitted to IRBs/IECs.

2. **Rationale**
   The changes detailed below address comments raised by the FDA and include other editorial changes or clarifications by the Sponsor.

3. **Summary of Changes**
   The following revisions were made to the protocol in Protocol Version 2.

(Note: Differences have been indicated in bold font.)

Section	Original Text	Revised Text
Page 1	**Original** Version: **06 Jun** 2014	Version **2: 24 September** 2014
Synopsis, Planned Number of Trial Sites	Approximately **30** (Europe and United States [US])	Approximately **35** (Europe and United States [US])
Synopsis, Methodology, *LTSE,* 2nd paragraph	Upon a subject's completion **of the Week 24 visit, at the end** of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase.	Upon a subject's completion **of the DB phase**, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase.
Synopsis, Methodology, LTSE, 4th paragraph	During the LTSE phase, subjects may titrate to higher doses of OCA, at a frequency not greater than **monthly**, up to a maximum **daily** dose of 10 mg daily.	During the LTSE phase, subjects may titrate to higher doses of OCA, at a frequency not greater than **3 monthly (ie, at each of the scheduled visits)**, up to a maximum dose of 10 mg daily.
Synopsis, Trial Design Schematic		
Synopsis, Inclusion Criterion #3	Cholangiography, or other appropriate imaging modality, within 12 months of Day 0 consistent with a diagnosis of PSC.	**Must have a diagnosis of PSC (based on cholangiography at any point in time) and must have had a cholangiography within the past 12 months.**

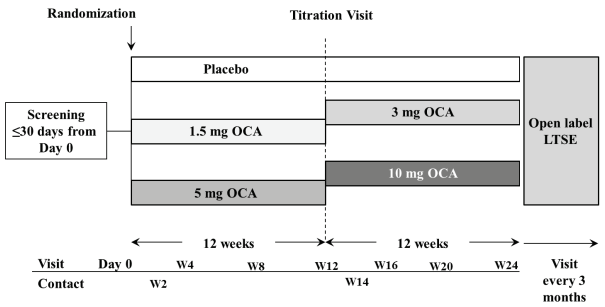
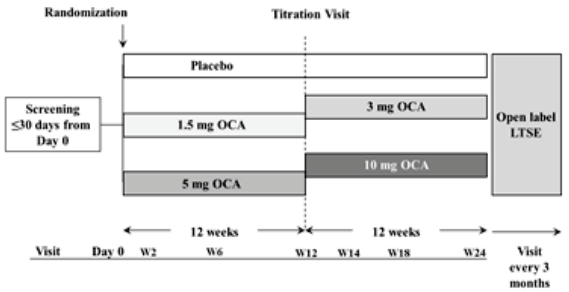
Section	Original Text	Revised Text
Synopsis, Inclusion Criterion #5	**Note 2: Subjects with documented Gilbert's syndrome may be allowed to participate in the study after discussion with the medical monitor.**	*Note 2* has been deleted from this section and moved to Synopsis, Exclusion Criterion #10 (see below).
Synopsis, Inclusion Criterion #6	For subjects with concomitant IBD: colonoscopy within 12 months of Day 0 confirming no dysplasia or colorectal cancer	For subjects with concomitant IBD: **a.** Colonoscopy within 12 months of Day 0 confirming no dysplasia or colorectal cancer **b. Subjects with Crohn's Disease (CD) must be in remission as defined by a Crohn's Disease Activity Index (CDAI) <150.** **c. Subjects with ulcerative colitis (UC) must either be in remission or have mild disease. Remission is defined as a partial Mayo score of ≤2 with no individual sub-score exceeding 1. Mild disease is defined as a partial Mayo score ≤3 with no individual sub-score exceeding 1 point.**
Synopsis, Inclusion Criterion #7	Note **3**:	Note **2**:
Synopsis, Inclusion Criterion #9	Contraception: female subjects of childbearing potential must use ≥1 effective **(≤1% failure rate)** method of contraception during the trial and until 4 weeks following the last dose of IP (including LTSE doses).	Contraception: female subjects of childbearing potential must use ≥1 effective method of contraception during the trial and until 4 weeks following the last dose of IP (including LTSE doses).
Synopsis, Exclusion Criterion #3	Exclusion criterion has been added/inserted; all other criteria numbering has subsequently shifted.	**Small duct cholangitis in the absence of large duct disease**
Synopsis, Exclusion Criterion #4	Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including:	Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including:

Section	Original Text	Revised Text
	(Change to 7th bullet, only.) • **Current splenomegaly as evidenced by ultrasound or platelets <50 x10^9/L**	*(Change to 7th bullet, only.)* • **Platelet count <50 x 10^9/L**
Synopsis, Exclusion Criterion #8	History of **any** bowel resection **unless permitted with prior discussion and written approval from Sponsor medical monitor**	History of **small** bowel resection
Synopsis, Exclusion Criterion #9	History of other chronic liver diseases, … non-alcoholic fatty liver disease (NAFLD), hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA) and hepatitis C virus	History of other chronic liver diseases … non-alcoholic fatty liver disease (NAFLD), **autoimmune hepatitis** , hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA) and hepatitis C virus
Synopsis, Exclusion Criterion #10	Moved from Synopsis, Inclusion Criterion # 5, which previously read: **Note 2: Subjects with documented Gilbert's syndrome may be allowed to participate in the study after discussion with the medical monitor.**	**Known Gilbert's syndrome or elevations in unconjugated (indirect) bilirubin >ULN**
Synopsis, Exclusion Criterion #14	Exclusion criterion inserted.	**Administration of antibiotics is prohibited ≤1 month of Day 0.**
Synopsis, Exclusion Criterion #15	Administration of the following medications is prohibited ≤6 months of Day 0 and **throughout the DB phase of the trial**: ... or nitrofurantoin).	Administration of the following medications is prohibited ≤6 months of Day 0 **and throughout the trial**: … or nitrofurantoin).
Synopsis, Exclusion Criterion #16	IBD flare during Screening (up to and including Day 0).	IBD flare during Screening (up to and including Day 0), **where "flare" is defined as follows:** • **UC flare: partial Mayo Score ≥5, and** • **CD flare: CDAI ≥250**

Section	Original Text	Revised Text
Synopsis, Criteria for Evaluation: Disease Specific Symptoms	Two additional items added	**Pruritus 5-D questionnaire** **Crohn's disease activity index (CDAI)**
Synopsis, Statistical Methods: Efficacy Analyses	The **co-primary efficacy endpoints are the absolute changes from Baseline in ALP at Week 12 and Week 24.** The primary efficacy analysis at Week 12 will compare the absolute change from Baseline in ALP between OCA treatment groups (**1.5 mg and 5 mg**) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. The primary efficacy analysis at Week 24 will compare the absolute change from Baseline in ALP between OCA treatment groups (3 mg and 10 mg) and placebo using the same ANCOVA model as the Week 12 analysis. **The co-primary endpoints will be tested using a hierarchical approach to control the overall significance level for multiple visit and dose comparisons.** **Secondary efficacy analyses of hepatic biochemistry and function parameters will use the same ANCOVA models as the primary endpoints.** In addition, secondary efficacy **analysis** of ALP response rates, defined as ALP to <1.5x ULN, will compare OCA	The primary **efficacy endpoint is the Week 24 change from Baseline in ALP. The primary efficacy analysis will compare the Week 24 change from Baseline in ALP between the OCA 10 mg treatment group** and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. **Secondary efficacy analyses of hepatic biochemistry and function parameters will use the same ANCOVA models as the primary endpoints. A hierarchical approach will be used for multiplicity adjustments. If the primary efficacy analysis is statistically significant ($p < 0.05$), the following order will be used in the testing procedure to compare the change from Baseline in ALP between OCA and placebo:** • **Week 12: OCA 5 mg treatment group (randomized to 5 mg for the initial 12 weeks followed by 10 mg for the latter 12 weeks) vs. placebo** • **Week 24: OCA 3 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo**

Section	Original Text	Revised Text
	treatment groups **and** placebo at Week 12 and Week 24 using a Cochran Mantel-Haenszel test stratified by the randomization stratification factor. Missing values **are** considered a non-response.	• **Week 12: OCA 1.5 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo** **If at any step the comparison is not statistically significant, then all subsequent comparisons will be exploratory rather than confirmatory.** In addition, secondary efficacy analyses of ALP response rates, defined as ALP to <1.5x ULN, will compare OCA treatment groups **vs.** placebo at Week 12 and Week 24 using a Cochran Mantel-Haenszel test stratified by the randomization stratification factor. Missing values **will be** considered a non-response. **An unblinded interim analysis for planning purposes will be conducted after approximately 50% of patients have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint, the change from Baseline in ALP, between OCA treatment groups (1.5 mg and 5 mg) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. No adjustments to the alpha level will be made.**

Section	Original Text	Revised Text
Synopsis, Statistical Methods: Safety Analyses, 2nd paragraph	… The absolute change from Baseline will also be summarized.	**... The change** from Baseline will also be summarized.
Synopsis, Statistical Methods: PK and PD Analyses	The pharmacokinetics (PK) of OCA and other bile acids will be evaluated, including AUC_t, C_{max}, t_{max}**, etc.**	The pharmacokinetics (PK) of OCA and other bile acids will be evaluated, including AUC_t, C_{max}, **and** t_{max},
Synopsis, Statistical Methods: Sample Size Justification	A sample size of 25 subjects per treatment group, a total of 75 subjects, will provide at least **95%** power to detect a treatment difference for change in ALP assuming the mean **percentage change** in ALP for OCA and…	A sample size of 25 subjects per treatment group, a total of 75 subjects, will provide at least **90%** power to detect a treatment difference for change in ALP assuming the mean **absolute change** in ALP for OCA and….
List of Abbreviations	New text inserted Text correction: IgG4: **i**mmunoglobulin G4	CD: Crohn's disease CDAI: Crohn's disease activity index UC: ulcerative colitis IgG4: **I**mmunoglobulin G4
5.5, 2nd paragraph	An increase in liver function tests … that are several fold higher **(20 to 50 mg daily)** than those studied in this protocol (1.5 mg, 3 mg, 5 mg, and 10 mg) doses.	An increase in liver function tests …. that are several fold higher (**primarily** 20 to 50 mg daily) than those studied in this protocol (1.5 mg, 3 mg, 5 mg, and 10 mg) doses.
7.1, LTSE, 2nd paragraph	Upon a subject's completion **of the Week 24 visit, at the end of the DB phase**, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase.	Upon a subject's completion **of the DB phase**, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase.

Section	Original Text	Revised Text
7.1.1, Figure 1		
Table 1, Visit Type & Visit Windows	Screening ≤30d D 0 **Contact W2 ± 3d** **Visit W4 ± 1wk** **Visit W8 ± 1wk** Visit W12 ± 1wk **Contact W14 ± 1wk** **Visit W16 ± 1wk** **Visit W20 ± 1wk** Visit W24/LTSE D1/EOT ± 1wk FU	Screening ≤30d D 0 **Visit W2 ±3d** **Visit W6 ±1wk** Visit W12 ±1wk **Visit W14 ±1wk** **Visit W18 ±1wk** Visit W24/LTSE D1/EOT ±1wk FU ±1wk
Table 1	New procedures added	**Partial Mayo Score (Screening visit & follow-up visit)** **CDAI (all visits)**
Table 1	Pruritus VAS	Pruritus VAS **and 5-D**
Table 1, Laboratory Evaluations	**Serum** Bile Acids	**Plasma** Bile Acids

Section	Original Text	Revised Text
Table 1, footnote b	Week 2 and 14 visits are contacts to assess AEs and treatment compliance; these are not clinic visits.	Week 12 is the Dose Titration Visit.
Table 1, footnote j	TE: at trial sites where the Fibroscan® TE device is available.	**Partial Mayo score completed only for subjects with UC.**
Table 1, footnote l	Questionnaire completed with input from the subject.	**CDAI completed only for subjects with CD.**
Table 1, footnote q	IP accountability/compliance will include review of tablets and bottles dispensed and returned at each clinic visit. **For subject contacts (ie, non-clinic visits), compliance with dosing and evaluation of missed doses should be discussed with the subject.**	IP accountability/compliance will include review of tablets and bottles dispensed and returned at each clinic visit.
Table 1, footnote t	For female subjects of child bearing potential, a urine β-hCG test is used. If the urine test is positive, it is to be repeated as a serum pregnancy test. See Section 8.1 for procedures to be followed for a subject whose pregnancy is early terminated and wishes to continue in the trial.	**Other analytes includes an additional blood sample for exploratory analysis.**
Table 1, footnote u	Fecal sample: for measurement of calprotectin and gut fecal microbiome; provision of a fecal sample by subjects is not mandatory. The subject should be instructed to collect a fecal sample within 2 days of the scheduled visit, as described in the laboratory manual.	**PK samples will be collected from those subjects who have consented for PK sampling procedures.**
Table 1, footnote k	New footnote	**Subjects with UC and CD will be asked to complete a diary recording details of their symptoms in the 7 days prior to their next scheduled visit.**
Table 2	New procedures added	**Partial Mayo Score (M3, M9, M15, M21 & Follow-Up Visit)** **CDAI (all visits)**

Section	Original Text	Revised Text
Table 2	Pruritus VAS	Pruritus VAS **and 5-D**
Table 2, Laboratory Evaluations	**Serum** Bile Acids & C4	**Plasma** Bile Acids & C4
Table 2, footnote i	Questionnaire completed with input from the subject.	**Partial Mayo score completed only for subjects with UC.**
Table 2, footnote k	IP accountability / compliance will include review of tablets and bottles dispensed and returned at each clinic visit.	**CDAI completed only for subjects with CD.**
Table 2, footnote o	Fecal sample: for measurement of calprotectin and gut fecal microbiome; provision of a fecal sample by subjects is not mandatory. The subject should be instructed to collect a fecal sample within 2 days of the scheduled visit, as described in the laboratory manual.	**Other analytes includes an additional blood sample for exploratory analysis.**
Table 2, footnote j	New footnote	**Subjects with UC and CD will be asked to complete a diary recording details of their symptoms in the 7 days prior to their next scheduled visit.**
7.4.2, 3rd paragraph	During the LTSE phase subjects may titrate to higher doses of OCA, at a frequency not greater than **monthly**, up to a maximum dose of 10 mg daily.	During the LTSE phase subjects may titrate to higher doses of OCA, at a frequency not greater than **3 monthly (ie, at each of the scheduled visits),** up to a maximum dose of 10 mg daily.

Section	Original Text	Revised Text
7.4.3	Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability.	Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability. **At a minimum, the occurrence of two life threatening serious adverse events (SAEs) or an SAE resulting in death will trigger an unscheduled and unblinded review of the data by the DSMC to determine if the trial should continue.**
8.2, Inclusion Criterion #3	Cholangiography, or other appropriate imaging modality, within 12 months of Day 0 consistent with a diagnosis of primary sclerosing cholangitis	**Must have a diagnosis of PSC (based on cholangiography at any point in time) and must have had a cholangiography within the past 12 months.**
8.2, Inclusion Criterion #5	Note 2: Subjects with documented Gilbert's syndrome may be allowed to participate in the study after discussion with the medical monitor.	*Note 2* has been deleted from this section and moved to Synopsis, Exclusion Criterion #10 (see below).
8.2, Inclusion Criterion #6	For subjects with concomitant IBD: colonoscopy within 12 months of Day 0 confirming no dysplasia or colorectal cancer	For subjects with concomitant IBD: a. Colonoscopy within 12 months of Day 0 confirming no dysplasia or colorectal cancer **b. Subjects with Crohn's Disease (CD) must be in remission as defined by a Crohn's Disease Activity Index (CDAI) <150.** **c. Subjects with ulcerative colitis (UC) must either be in remission or have mild disease. Remission is defined as a partial Mayo score of ≤2 with no individual sub-score exceeding 1. Mild disease is defined as a partial Mayo score ≤3 with no individual sub-score exceeding 1 point.**
8.2, Inclusion Criterion #7	Note **3**:	Note **2**:

Section	Original Text	Revised Text
8.2, Inclusion Criterion #9	Contraception: female subjects of childbearing potential must use ≥1 effective **(≤1% failure rate)** method of contraception during the trial and until 4 weeks following the last dose of IP (including LTSE doses).	Contraception: female subjects of childbearing potential must use ≥1 effective method of contraception during the trial and until 4 weeks following the last dose of IP (including LTSE doses).
8.2, Exclusion Criterion #3	Exclusion criterion has been added/inserted; all other criteria numbering has subsequently shifted.	**Small duct cholangitis in the absence of large duct disease**
8.2, Exclusion Criterion #4	Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including: *(Change to 7th bullet, only.)* • **Current splenomegaly as evidenced by ultrasound or platelets <50 x 10^9/L**	Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including: *(Change to 7th bullet, only.)* • **Platelet count <50 x 10^9/L**
8.2, Exclusion Criterion #8	History of **any** bowel resection **unless permitted with prior discussion and written approval from Sponsor medical monitor**	History of **small** bowel resection
8.2, Exclusion Criterion #9	History of other chronic liver diseases, … non-alcoholic fatty liver disease (NAFLD), hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA) and hepatitis C virus	History of other chronic liver diseases, … non-alcoholic fatty liver disease (NAFLD), **autoimmune hepatitis** , hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA) and hepatitis C virus
8.2, Exclusion Criterion #10	Moved from Synopsis, Inclusion Criterion # 5, which previously read: **Note 2: Subjects with documented Gilbert's syndrome may be allowed to participate in the study after discussion with the medical monitor.**	**Known Gilbert's syndrome or elevations in unconjugated (indirect) bilirubin >ULN**
8.2, Exclusion Criterion #14	Exclusion criterion inserted.	**Administration of antibiotics is prohibited ≤1 month of Day 0.**

Section	Original Text	Revised Text
8.2, Exclusion Criterion #15	Administration of the following medications is prohibited ≤6 months of Day 0 and **throughout the DB phase of the trial**: ... or nitrofurantoin).	Administration of the following medications is prohibited ≤6 months of Day 0 and **throughout the trial**: … or nitrofurantoin).
8.2, Exclusion Criterion #16	IBD flare during Screening (up to and including Day 0).	IBD flare during Screening (up to and including Day 0), **where 'flare' is defined as follows:** • **UC flare: partial Mayo Score ≥5, and** • **CD flare: CDAI ≥250**
8.4.1, Clinical Laboratory Values, 2nd bullet	Two consecutive measurements of **conjugated (direct) bilirubin >2x ULN** AND >2x the Baseline value in the absence of evidence of new biliary obstruction.	Two consecutive measurements of **total bilirubin >ULN** AND >2x the Baseline value in the absence of evidence of new biliary obstruction.
8.4.1, IBD Flares (new section)	New text inserted into protocol.	**Subjects who experience 3 or more IBD flare-ups in one year during the study will be discontinued, where 'flare' is defined as follows:** • **for UC flare: as a partial Mayo Score ≥5, and** • **for CD flare: as a CDAI ≥250** **Section 8.4.2 below describes treatment guidelines for managing IBD flares during the study.**
8.4.2, 1st paragraph	The following events are considered appropriate reasons for a subject to discontinue from the trial:	The following events are considered appropriate **(potential)** reasons for a subject to discontinue from the trial:
8.4.2, Bactierial Cholangitis	… in conjunction with clinical signs and symptoms and positive diagnostic imaging tests. **Subjects should temporarily interrupt treatment with IP and receive standard of care treatment. Use of amoxicillin/clavulanate is discouraged, but these may be used if there are no other treatment options; this**	... in conjunction with clinical signs and symptoms and positive diagnostic imaging tests. **Local guidelines should be followed for the management of patients with acute bacterial cholangitis. In the absence of such local guidelines, the following guidelines should**

Section	Original Text	Revised Text
	should be discussed with the medical monitor in advance of a decision to treat with these medications. Discontinuation from the trial is not mandatory in cases of bacterial cholangitis unless signs and symptoms do not resolve within a clinically reasonable timeframe (within 1 month or as agreed upon with the medical monitor) or the cholangitis becomes life threatening in the opinion of the investigator or medical monitor. In any event, IP should not be restarted until signs and symptoms have resolved and the subject's liver biochemistry has returned to pre-cholangitis levels. A subject with **frequent (frequency as judged by the investigator and with input from the medical monitor)** bacterial cholangitis events should be discontinued from the trial.	**be followed if acute cholangitis is suspected**: • **Diagnosis of acute cholangitis should be established based on a combination of typical clinical features, laboratory data, and imaging findings. Subsequent to an intervention to relieve biliary obstruction acute cholangitis may occur with typical signs and symptoms including intermittent fever with chills, right upper quadrant pain, and jaundice (also known as the Charcot triad). Further confirmation of the diagnosis should then be made via laboratory data (eg, elevated C-reactive protein levels and/or leukocytosis) and abdominal imaging tests (magnetic resonance cholangiopancreatography; MRCP).** • **Treatment of acute cholangitis should be directed towards treatment of the biliary infection and relieving obstruction. Therefore, treatment is comprised of systemic antibiotic therapy and biliary drainage procedures, with appropriate supportive care.** • **Antibiotic agents should be administered empirically as early as possible. Blood and bile cultures should also be performed at the earliest opportunity and prior to initiating antibiotic treatment, if possible.** • **The selection of an antibiotic agent should be based on likely infecting bacteria, the**

Section	Original Text	Revised Text
		severity of the disease, and the presence of comorbidities. Empiric antibiotic agents may be replaced by directed therapies once the blood and bile culture results become available. The use of amoxicillin/clavulanate and other antibiotic treatments with potential for hepatotoxicity should be avoided. **Subjects should temporarily interrupt treatment with IP and receive standard of care treatment. Discontinuation from the trial is not mandatory in cases of bacterial cholangitis unless signs and symptoms do not resolve within a clinically reasonable timeframe (typically within 1 month or as agreed upon with the medical monitor) or the cholangitis becomes life threatening in the opinion of the investigator or medical monitor. In any event, IP should not be restarted until signs and symptoms have resolved and the subject's liver biochemistry has returned to pre-cholangitis levels.** A subject with **3 bacterial cholangitis events in one year during the study** should be discontinued from the trial.
8.4.2, IBD Flare	If a subject experiences an IBD flare during the trial (post-Day 0), he/she may remain on IP but this should be discussed with the medical monitor.	If a subject experiences an IBD flare during the trial (post-Day 0), he/she may remain on IP but this should be discussed with the medical monitor **and IBD flares should be treated as follows (but adjusted based upon local guidelines and standards of care, disease severity and personal patient preferences, as appropriate): aminosalicylates alone (high dose if appropriate) or with a topical aminosalicylate and/or topical, oral, or**

Section	Original Text	Revised Text
		intravenous corticosteroids or immunosuppressant therapy, including anti-TNF therapy. Surgery may be required in severe cases that are refractory to medicinal treatment. **Subjects who experience 3 or more IBD flare-ups in 1 year during the study will be discontinued.**
9.2.3, 1st bullet	New bullet point inserted under 1st bullet point	Administration of antibiotics within 1 month of Day 0, except if administered for acute cholangitis whereby its use is prohibited within 3 months of Day 0. NOTE: Antibiotics are permitted as required during participation in the trial except amoxicillin/clavulanate (Augmentin) which has restrictions as detailed below.
9.2.3, 3rd bullet	• Prohibited from 6 months prior to Day 0 and throughout the **DB** phase of the trial **(these are not prohibited during the LTSE): …** -Amoxicillin/clavulanate should not be used unless there are no other treatment options (this should be discussed with the medical monitor in advance of their use in this situation, where possible)	• Prohibited from 6 months prior to Day 0 and throughout the **LTSE** phase of the trial **unless as noted to discuss with Medical Monitor**: … -Amoxicillin/clavulanate (**Augmentin**) should not be used unless there are no other treatment options (this should be discussed with the medical monitor in advance of their use in this situation, where possible). **Augmentin is also discouraged in the treatment of cholangitis but is not outright excluded (Section 8.4.2).**
9.4, 1st paragraph	At Day 0, after review … treatment groups in a 1:1:1 **ratio across sites based** on … LTSE phase.	At Day 0, after review … treatment groups in a 1:1:1 **ratio based** on … LTSE phase.

Section	Original Text	Revised Text
9.6.1, 1st paragraph	All trial visits during the DB period are relative to Day 0 (eg, if the **Week 4** visit occurs 4 days late, the **Week 8** visit should still be **8** weeks from Day 0). The Screening visit should occur ≤30 days prior to the Day 0 visit. All visits **and contacts** during the DB treatment period should occur within ± 1 week of the indicated time. The exception to this is **the contact** at Week 2, which should occur within ± 3 days of the indicated time.	All trial visits during the DB period are relative to Day 0 (eg, if the **Week 6** visit occurs 4 days late, the **Week 12** visit should still be **12** weeks from Day 0). The Screening visit should occur ≤30 days prior to the Day 0 visit. All visits during the DB treatment period should occur within ±1 week of the indicated time. The exception to this is the Week 2 visit, which should occur within ±3 days of the indicated time.
9.6.3, 9th bullet	New bullet 9.	**For subjects with UC): provide the diary and request subject completes this for each of the 7 consecutive days prior to the next scheduled visit.**
9.6.3, 10th bullet	New bullet 10.	**For subjects with CD: provide the diary and request subject completes this for each of the 7 consecutive days prior to the next scheduled visit.**
9.6.3, 11th bullet	... no more than 25% of subjects recruited will have a bilirubin >1.5x ULN and <2.5x ULN). **In addition, subjects with documented Gilbert's syndrome may be allowed to participate in the study after discussion with the medical monitor.**	… no more than 25% of subjects recruited will have a bilirubin >1.5x ULN and <2.5x ULN).
9.6.4, 5th bullet	Obtain Partial Mayo Scoring System for Assessment of Ulcerative Colitis Activity (partial Mayo score, excluding endoscopy). See Appendix B for details.	**For subjects with UC: obtain partial Mayo score (excluding endoscopy). See Appendix B for details.**
9.6.4, 6th bullet	New bullet 6	**For subjects with CD: complete CDAI assessments and assign CDAI score**. **See Appendix F for details.**
9.6.4, 7th bullet	Administer pruritus visual analogue scale (VAS) subject questionnaire. See Appendix C for details.	Administer pruritus visual analogue scale (VAS) subject questionnaire **and 5-D Itch Questionnaire**. See Appendix C for details.

Section	Original Text	Revised Text
9.6.4, 9th bullet, 5th sub-bullet	**Serum** bile acids and 7α-hydroxy-4-cholesten-3-one (C4)	**Plasma** bile acids and 7α-hydroxy-4-cholesten-3-one (C4)
9.6.3, 15th bullet	New bullet 15.	Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.
9.6.4, 16th bullet	Reiterate dosing instructions and advise the subject: - All subjects are to … Further details are included in Section 9.1. **Book the date and time for the Week 2 Contact.**	Reiterate dosing instructions and advise the subject: -All subjects are to … Further details are included in Section 9.1. **-NOT to take IP on the morning of the next trial visit, and** **-To bring the IP bottle(s) and** **-To fast overnight (at least 8 hours) prior to the next trial visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.**
9.6.5	**Week 2 Contact Procedures** The Week 2 contact is not a clinic visit however, the site is required to contact the subject to assess the following: • Assess and record AEs • Record current concomitant medications • Assess IP compliance • Reiterate dosing instructions and advise the subject: -NOT to take IP on the morning of the next trial visit,	**Week 2 Procedures** • Assess and record AEs • Record current concomitant medications • **Record vital signs** • **For subjects with UC: obtain partial Mayo score (excluding endoscopy)** • **For subjects with CD: complete CDAI assessments and assign CDAI score**

	and -To bring the IP bottle(s) and -To fast overnight (at least 8 hours) prior to the next trial visit. Fasting is required prior to all trial visits, but water is permitted.	• **Administer pruritus VAS subject questionnaire and 5-D Itch Questionnaire** • **Obtain blood samples for serum chemistry and hematology** • **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 trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.** • Assess IP compliance **and perform accountability; retrieve used bottles and document returns** • **Record the visit in IWRS and dispense indicated bottles of IP** • **Provide the diary and request this is completed for 7 consecutive days prior to the next scheduled visit.** • Reiterate dosing instructions and advise the subject: -NOT to take IP on the morning of the next trial visit, and -To bring the IP bottle(s); and -To fast overnight (at least 8 hours) prior to the next trial visit. Fasting is required prior to all trial visits, but water is permitted**, and the subject should dose**

Section	Original Text	Revised Text
		at the visit after all assessments have been performed.
9.6.6, title	Week **8** Procedures	Week **6** Procedures
9.6.6, 4th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC:** obtain partial Mayo score (excluding endoscopy)
9.6.6, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.6, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.6, 8th bullet, 2nd sub-bullet	… fasting is required prior to all trial visits, but water is permitted.	… fasting is required prior to all trial visits, but water is permitted, **and the subject should dose at the visit after all assessments have been performed.**
9.6.6, 11th bullet	New bullet 11	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.6, 12th bullet, 3rd sub-bullet	… Fasting is required prior to all trial visits, but water is permitted.	… Fasting is required prior to all trial visits, but water is permitted, **and the subject should dose at the visit after all assessments have been performed.**
9.6.7, 4th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC:** obtain partial Mayo score (excluding endoscopy)
9.6.7, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.7, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**

Section	Original Text	Revised Text
9.6.7, 7th bullet, 5th sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.7, 12th bullet, 2nd sub-bullet	… fasting is required prior to all trial visits, but water is permitted.	… fasting is required prior to all trial visits, but water is permitted, **and the subject should dose at the visit after all assessments have been performed.**
9.6.7, 15th bullet	New bullet 15	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.7, 16th bullet	Reiterate dosing instructions **Book the date and time for the Week 14 contact telephone call.**	Reiterate dosing instructions **and advise the subject:** **-NOT to take IP on the morning of the next visit, and** **-To bring the IP bottle(s) and** **-To fast overnight (at least 8 hours) prior to the next visit. Fasting is required prior to all trial visits, but water is permitted, and the subject should dose at the visit after all assessments have been performed.**
9.6.8, title	Week **16** Procedures	Week **14** Procedures
9.6.8, 4th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.8, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.8, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**

Section	Original Text	Revised Text
9.6.8, 8th bullet, 2nd sub-bullet	… fasting is required prior to all trial visits, but water is permitted.	… fasting is required prior to all trial visits, but water is permitted, **and the subject should dose at the visit after all assessments have been performed.**
9.6.8, 11th bullet	New bullet 11	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.9, title	Week **20** Procedures	Week **18** Procedures
9.6.9, 4th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.9, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.9, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.9, 8th bullet, 2nd sub-bullet	… fasting is required prior to all trial visits, but water is permitted.	… fasting is required prior to all trial visits, but water is permitted, **and the subject should dose at the visit after all assessments have been performed.**
9.6.9, 11th bullet	New bullet 11	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.10, 8th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.10, 9th bullet	New bullet 9	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.10, 10th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**

Section	Original Text	Revised Text
9.6.10, 12th bullet, 5th sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.10, For Subjects Participating in the LTSE, 5th bullet	New bullet 5	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.10, For Subjects Participating in the LTSE, 6th bullet, 3rd sub-bullet	… Fasting is required prior to all trial visits, but water is permitted.	… Fasting is required prior to all trial visits, but water is permitted **and the subject should dose at each visit after all assessments have been performed.**
9.6.10, For Subjects NOT Participating in the LTSE, 3rd bullet	New bullet 3	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.11, 8th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.11, 9th bullet	New bullet 9	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.11, 10th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**

Section	Original Text	Revised Text
9.6.11, 12th bullet, 5th sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.11, 13th bullet	New bullet 13	**For sites participating in PK sampling: obtain samples for PK analysis (see section 11.5 for sampling schedule)**
9.6.11, 19th bullet	New bullet 19	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.12, 4th bullet	New bullet 4	**For subjects with UC: obtain partial Mayo score (excluding endoscopy)**
9.6.12, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.12, 5th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.14	See **Section 9.6.12** for the LTSE Day 1 (DB Week 24 visit) procedures.	See **Section 9.6.10** for the LTSE Day 1 (DB Week 24 visit) procedures.
9.6.15, 4th bullet	New bullet 4	**For subjects with UC: obtain partial Mayo score (excluding endoscopy)**
9.6.15, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.15, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.15, 12th bullet	New bullet 12	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**

Section	Original Text	Revised Text
9.6.16, 4th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.16, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.16, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.16, 7th bullet, 3rd sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.16, 13th bullet	New bullet 13	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.17, 6th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.17, 7th bullet	New bullet 7	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.17, 8th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.17, 9th bullet, 5th sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.17, 16th bullet	New bullet 16	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.18, 4th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)

Section	Original Text	Revised Text
9.6.18, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.18, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.18, 13th bullet	New bullet 13	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.19, 8th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.19, 9th bullet	New bullet 9	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.19, 10th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
9.6.19, 12th bullet, 5th sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.19, 19th bullet	New bullet 19	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.20, 8th bullet	Obtain partial Mayo score (excluding endoscopy)	**For subjects with UC**: obtain partial Mayo score (excluding endoscopy)
9.6.20, 9th bullet	New bullet 9	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.20, 10th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**

Section	Original Text	Revised Text
9.6.20, 12th bullet, 5th sub-bullet	**Serum** bile acids and C4	**Plasma** bile acids and C4
9.6.20, 13th bullet	New bullet 17	**Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.**
9.6.21, 4th bullet	New bullet 4	**For subjects with UC: obtain partial Mayo score (excluding endoscopy)**
9.6.21, 5th bullet	New bullet 5	**For subjects with CD: complete CDAI assessments and assign CDAI score**
9.6.21, 6th bullet	Administer pruritus VAS subject questionnaire	Administer pruritus VAS subject questionnaire **and 5-D Itch questionnaire**
11.3, Disease Specific Symptoms, 1st paragraph	Disease-specific symptoms of IBD and pruritus will be assessed using the partial Mayo score and as a Pruritus VAS respectively.	Disease-specific symptoms of IBD and pruritus will be assessed using the partial Mayo score **(only for subjects with UC)**, **CDAI (only for subjects with CD)** and as a Pruritus VAS and **5-D itch questionnaire** respectively.
11.3 Disease Specific Symptoms, IBD Symptoms, CDAI	New paragraph inserted	**The CDAI will be performed by the investigator at specified visits to assess symptoms associated with CD (Best 1976) and will be based on the subject's recount of their symptoms in addition to hematocrit and body weight measurements. Details of the CDAI are shown in Appendix F.** **To assist sites with recording and calculating the partial Mayo score and the CDAI subjects with UC & CD, respectively, will be asked to complete a diary in the 7 days prior to their next scheduled trial visit to record their relevant symptoms. The PI will transcribe relevant information in to the subject's**

Section	Original Text	Revised Text
		medical records for SDV and retain the diary cards. Pertinent aspects of these data will be recorded in the CRF.
11.3, Disease Specific Symptoms, Pruritus	Subjects will be asked to complete the Pruritus VA … Details of the Pruritus VAS are shown in Appendix C.	**In addition to the assessment of pruritus as an AE with mild, moderate and severe categories, pruritus will be specifically assessed by patient questionnaires:** • Pruritus VAS Subjects will be asked to complete the Pruritus … Details of the Pruritus VAS are shown in Appendix C. • 5-D Itch 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).**
11.4, paragraph 3	New paragraph inserted	**Exploratory Analytes** **Blood samples for future analysis related to the effects of OCA or FXR activation will be collected at specified timepoints during the study and may be assayed on an exploratory research basis. The samples will be stored for up to 2 years after the end of the study.**
11.5, 4th paragraph	Subjects should not drink additional water for 1 hour after taking the dose of IP **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 nutrition information that has been and submitted to and approved by the Sponsor in advance.**	Subjects should not drink additional water for 1 hour after taking the dose of IP. **After approximately 1 hour postdose, subjects will be fed a standardized meal consisting of a Nutridrink™ (Nutricia).**

Section	Original Text	Revised Text
12.1.1.2, 2nd paragraph	2nd paragraph added to this section	**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.**
12.1.5	**Expected Serious Adverse Events** There are a number of events which are commonly associated with PSC and for reporting purposes, these events are considered to be 'Expected' in this patient population:	**Anticipated Serious Adverse Events Associated with PSC** There are a number of events which are commonly associated with PSC and for **the Sponsor's Regulatory** reporting purposes, these events are considered to be 'Expected' in this patient population **and are listed below**. **The investigator remains responsible for reporting to the Sponsor all SAEs including the events identified here:**
12.2.1	… Demographic characteristics (age, gender, race, ethnicity, etc) will be recorded.	… Demographic characteristics (age, gender, race, ethnicity, etc) will be recorded, **as will any historical or on study data on colonoscopies (mucosal and histological) within the last 3 years and prior and on study liver biopsies, hepatic imaging, etc. Reports should be available in the source data.**
12.2.2	… If clinically significant abnormalities are observed before administration of the first dose of IP on Day 1**, they should be reported in the subject's medical history.**	… If clinically significant abnormalities are observed before administration of the first dose of IP on Day 1, **they should be reported as adverse events.**

Section	Original Text	Revised Text
12.2.4	Any clinically significant abnormalities on ECGs recorded after **Day 0** will also be documented as AEs and entered on the AE page of the CRF.	Any clinically significant abnormalities on ECGs recorded after **Screening** will also be documented as AEs and entered on the AE page of the CRF.
12.2.5. 1st bullet point	Hematology (hemoglobin, hematocrit, white blood cell [WBC] count with differential, platelets, red blood cell [RBC] count)	Hematology **and Coagulation** (hemoglobin, hematocrit, white blood cell [WBC] count with differential, platelets, red blood cell [RBC] count, **INR, prothrombin time , partial thromboplastin time**)
13.2	A sample size of 25 subjects per treatment group, a total of 75 subjects, will provide at least **95%** power to detect a treatment difference for a change in ALP assuming a 20% dropout and the **mean** percentage changes … alpha level of 0.05.	A sample size of 25 subjects per treatment group, a total of 75 subjects, will provide at least **90%** power to detect a treatment difference for a change in ALP assuming a 20% dropout and the mean **absolute** changes … alpha level of 0.05.
13.3	One of the primary objectives of this proof of concept trial is to evaluate the efficacy of OCA in subjects with PSC. **Accordingly, the primary efficacy analysis will evaluate the absolute change from Baseline in ALP with each dose of OCA versus placebo.** The primary population for efficacy analyses **will use** the ITT population. Sensitivity analyses will be conducted using the Completer populations.	One of the primary objectives of this proof of concept trial is to evaluate the efficacy of OCA in subjects with PSC. The primary population for efficacy analyses **is** the ITT population. Sensitivity analyses will be conducted using the Completer populations.
13.3.1	The **co-primary** efficacy endpoints **are** the absolute changes from Baseline in ALP at **Week 12 and Week 24**. **The primary efficacy analysis at Week 12 will compare the change from Baseline in ALP between OCA treatment groups (1.5 mg and 5 mg) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. The primary efficacy analysis at Week 24 will compare the change from Baseline in ALP between OCA treatment groups (3 mg**	The **primary** efficacy endpoint **is** the **Week 24 change** from Baseline in ALP. The primary efficacy analysis **will compare the Week 24 change from Baseline in ALP between OCA 10 mg treatment group** and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate.

Section	Original Text	Revised Text
	and 10 mg) and placebo using the same ANCOVA model as the Week 12 analysis. **The co-primary endpoints will be tested using a hierarchical approach to control the overall significance level for multiple visit and dose comparisons.** The approach will be detailed in the SAP.	
13.3.2, 1st & 2nd paragraphs	Secondary efficacy analyses of hepatic **biochemistry and function parameters (eg, ALT, AST, and GGT) will use the same ANCOVA models as the primary endpoints. Hepatic biochemistry and function parameters** will be summarized by treatment group using … of all available evaluations prior to treatment.	Secondary efficacy analyses of hepatic biochemistry and function parameters (eg, ALT, AST, and GGT) will be summarized by treatment group using … of all available evaluations prior to treatment. **Hepatic biochemistry and function parameters will be analyzed using the same ANCOVA model as specified for the primary efficacy analysis.** **A hierarchical approach will be used for multiplicity adjustments. If the primary efficacy analysis is statistically significant (p <0.05), the following order will be used in the testing procedure to compare the change from Baseline in ALP between OCA and placebo:** • **Week 12: OCA 5 mg treatment group (randomized to 5 mg for the initial 12 weeks followed by 10 mg for the latter 12 weeks) vs. placebo** • **Week 24: OCA 3 mg treatment group (randomized to 1.5 mg for the initial 12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo** • **Week 12: OCA 1.5 mg treatment group (randomized to 1.5 mg for the initial**

Section	Original Text	Revised Text
		12 weeks followed by 3 mg for the latter 12 weeks) vs. placebo **If at any step a comparison above is not statistically significant, then all subsequent comparisons will be exploratory rather than confirmatory.**
13.3.2, 3rd paragraph	In addition, secondary efficacy **analysis** of ALP … stratification factor.	In addition, secondary efficacy **analyses** of ALP … stratification factor.
13.3.2, 4th paragraph	… The change from Baseline will be analyzed using an ANCOVA model with a fixed effect for treatment group and the Baseline values as a covariate.	… The change from Baseline will be analyzed using **the same** ANCOVA model **as specified for the primary efficacy analysis.**
13.3.2, 5th paragraph	5th paragraph added to this section	**Subgroup analyses will be evaluated as deemed appropriate, including but not limited to, those subjects who start antibiotics after first dose of investigational product.**
13.4, 1st paragraph	PK parameters will be determined for OCA, glyco-OCA, tauro-OCA, and total OCA (OCA plus conjugates). **The following** PK parameters will be calculated using non-compartmental methods where appropriate:	PK parameters will be determined for OCA, glyco-OCA, tauro-OCA, and total OCA (OCA plus conjugates). PK parameters, **including the following**, will be calculated using non-compartmental methods where appropriate:
13.4, 2nd paragraph	An **exploratory** exposure-response assessment will be made comparing … in this patient population.	An exposure-response assessment will be made comparing ... in this patient population.
13.5.2	Baseline values, the values at each visit … assessments by **treatment**. Baseline is defined as … treatment (except for lipoprotein assessments where Baseline **will be Day 0**).	Baseline values, the values at each visit … assessments by **treatment group.** Baseline is defined as … treatment (except for lipoprotein assessments where Baseline will be **the fasted** Day 0 **assessment**).
13.5.3	The change from Baseline will also be summarized.	The **absolute** change from Baseline will also be summarized.

Section	Original Text	Revised Text
13.6 & 13.6.1	**13.6 Interim Analysis** **A formal interim efficacy analysis (eg, at Week 12) is not planned. However,** once all subjects have completed the DB phase of the study, the DB database will be locked **and** unblinded **and analyses will performed**. The **specific details of the analyses** will be documented in the SAP.	13.6 Interim **Analyses and Data Monitoring** **13.6.1 Interim Analysis** *(new section)* **An unblinded interim analysis will be conducted after approximately 50% of subjects have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint, the change from Baseline in ALP, between OCA treatment groups and placebo. No adjustments to the alpha level will be made.** **In addition,** once all subjects have completed the DB phase of the study, the DB database will be **locked, unblinded, and full analyses will be performed.** The specific details of **both the interim and end of double-blind** analyses will be documented in the SAP.

Section	Original Text	Revised Text
13.6.2, 1st paragraph	Section 13.6.2 is a new section created to replace the previous Section 13.7 (Data Safety Monitoring Committee) that includes some of the original text of Section 13.7. **13.7 Data Safety Monitoring Committee** An independent DSMC will review safety data at periodic intervals **from this and other OCA trials**. Members of the DSMC will not be allowed to participate as investigators in this trial and will not otherwise consult for the Sponsor.	**13.6.2 Data and Safety Monitoring Committee** An independent DSMC will review safety data at periodic intervals **from this trial**. **The DSMC includes internationally recognized hepatologists, pharmaceutical physicians and statistician(s). 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 trial and will not otherwise consult for the Sponsor.
13.6.2, 2nd paragraph	The DSMC will review **safety data** … treatment of subjects.	The DSMC will review **data** … treatment of subjects.
13.6.2, 3rd paragraph	The DSMC operates under an appropriate charter … **that will define** its organization … each trial.	The DSMC operates under an appropriate charter … **that defines** its organization … each trial.
13.6.2, 4th & 5th paragraphs	Two new paragraphs inserted into this section.	**Data listings provided to the DSMC do not contain individual patient 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**

Section	Original Text	Revised Text
		treatment columns with 'dummy' labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA coded AEs, and AEs leading to early withdrawal of study drug. 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. At a minimum the occurrence of two life threatening SAEs or an SAE resulting in death will trigger an unscheduled and unblinded review of the data by the DSMC.**
19	New references inserted	**Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976 Mar; 70 (3): 439–444.** **Elman S, Hynan L, Gabriel V, et al. The 5-D itch scale: a new measure of pruritus. British Journal of Dermatology. 2010 Dec; 162: 587-593**
Appendix D	New appendix added	**5-D Itch Questionnaire included.**
Appendix F	New appendix added	**CDAI included**

APPENDIX H. PROTOCOL VERSION 3 – SUMMARY OF CHANGES

Background: Protocol 747-207 has been prepared as a Phase 2 trial to evaluate the potential clinical benefit of OCA in PSC.

Rationale: Version 3 of the protocol includes changes to clarify eligibility criteria, procedures, and minor editorial changes.

Summary of Changes: The following revisions were made to the Protocol Version 2 in Protocol Version 3. (Note: Deletions are stricken and additions are indicated in bold font.) Minor grammatical changes are not detailed unless included with other changes (eg, capitalizations, punctuation).

Section	Original Text	Revised Text
Cover Page	Original Version: 06 Jun 2014 Version 2: 24 September 2014	Original Version: 06 Jun 2014 Version 2: 24 September 2014 **Version 3: 26 August 2015**
Investigator's Agreement	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 747-207 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), ~~21CFR Part 312 and all applicable regulatory requirements~~.	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 747-207 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.**
Contact Information	Medical Monitor – 24 hour Emergency Reporting ~~Contact: Roya Hoosmand-Rad, MD, PhD~~ ~~Executive Director, Clinical Research~~ Mobile: ~~+1 858 880 6485~~ (Pacific Time Zone) ~~Telephone: +1 858 964 1571 (Pacific Time Zone)~~ Email: ~~rhooshmand-rad~~@interceptpharma.com Clinical Operations and Project Management Contact: Tessa Beecher-Jones BSc (Hons) ~~Head EU Clinical Operations~~ Telephone: +44 1491 640 710 (GMT) Mobile: +44 7969 621 504 (GMT) Email: tbeecherjones@interceptpharma.com	Medical Monitor – 24 hour Emergency Reporting Contact: Barbara Scholz, MD, MPH Mobile: +**1 844 250 6398** (Pacific Time Zone) Email: **barbara.scholz**@interceptpharma.com Clinical Operations and Project Management Contact: Tessa Beecher-Jones BSc (Hons) **VP, Head of Clinical Operations, EU** Telephone: +44 1491 640 710 (GMT) Mobile: +44 7969 621 504 (GMT) Email: tbeecherjones@interceptpharma.com

Section	Original Text	Revised Text
Synopsis, Long-Term Safety Extension Phase (LTSE)	Following completion of participation in the DB phase, subjects will ~~continue in the study in the~~ open-label long-term safety extension (LTSE) phase ~~for~~ a further 24 months~~, and will be required at this time to reconfirm their consent for participation in the trial~~. Upon a subject's completion of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA unless safety and tolerability warrant a dose reduction to 5 mg. ~~If an investigator does not wish for a subject to be titrated in line with the below schedule, this should be discussed with the medical monitor~~ • Placebo at end of DB → 5 mg OCA in LTSE • 3 mg OCA at end of DB → 5 mg OCA in LTSE • 10 mg OCA at end of DB → 10 mg OCA in LTSE Those subjects who did not up-titrate their dose at Week 12 in the DB phase can remain on their DB dose, or commence at 5 mg at the decision of the ~~i~~nvestigator based on safety and tolerability of the DB dose at Week 24.	Following completion of participation in the DB phase, subjects will **be asked to reconfirm their consent for participation** in the open-label long-term safety extension (LTSE) phase **(**a further 24 months**)**. Upon a subject's completion of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA unless safety and tolerability warrant a dose reduction to 5 mg. • Placebo at end of DB → 5 mg OCA in LTSE • 3 mg OCA at end of DB → 5 mg OCA in LTSE • 10 mg OCA at end of DB → 10 mg OCA in LTSE Those subjects who did not up-titrate their dose at Week 12 in the DB phase can remain on their DB dose, or commence at 5 mg at the decision of the **I**nvestigator based on safety and tolerability of the DB dose at Week 24. **If an Investigator does not wish for a subject to be titrated in line with the above schedules, this may be discussed with the Medical Monitor.**

Section	Original Text	Revised Text
	During the LTSE phase, subjects may titrate to higher doses of OCA, at a frequency not greater than 3 monthly (ie, at each of the scheduled LTSE visits), up to a maximum dose of 10 mg daily. The guideline for an increase in the dose of OCA is based on tolerability and the goal of achieving an ALP level <1.5x ~~the~~ ULN. Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to10 mg. The ~~i~~nvestigator may decrease the dose of OCA, or dosing frequency, in line with safety and tolerability as required for that subject. Following a change in OCA dose or dose frequency, an ~~i~~nvestigator may be permitted to return the subject to a prior dose or dosing frequency and this should be discussed with the Intercept ~~m~~edical ~~m~~onitor in advance. ~~A few Sponsor representatives may be unblinded during the trial. If there are any findings regarding safety, tolerability, or efficacy that indicate an alternative optimal LTSE starting dose, the starting dose in the LTSE may be reduced.~~	During the LTSE phase, subjects may titrate to higher doses of OCA, at a frequency not greater than 3 monthly (ie, at each of the scheduled LTSE visits), up to a maximum dose of 10 mg daily. The guideline for an increase in the dose of OCA is based on tolerability and the goal of achieving an ALP level <1.5x ULN. Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to10 mg. The **I**nvestigator may decrease the dose of OCA, or dosing frequency, in line with safety and tolerability as required for that subject. Following a change in OCA dose or dose frequency, an **I**nvestigator may be permitted to return the subject to a prior dose or dosing frequency and this should be discussed with the Intercept **M**edical **M**onitor in advance.
Synopsis Methodology, Inclusion Criteria and Section 8.2 Subject Inclusion Criteria	6. For subjects with concomitant IBD: a. Colonoscopy within 12 months of Day 0 confirming no dysplasia or colorectal cancer	6. For subjects with concomitant IBD: a. Colonoscopy **(if the subject has a colon) or other appropriate endoscopic procedure** within 12 months of Day 0 confirming no dysplasia or colorectal cancer

Section	Original Text	Revised Text
Synopsis Methodology, Inclusion Criteria and Section 8.2 Subject Inclusion Criteria	7. For subjects being administered UDCA as part of their standard of care, the dose must have been stable for ≥3 months prior to, and including, Day 0 and must not have exceeded 20 mg/kg/day during this time. Note 2: Subjects will be stratified according to UDCA use and no more than 50% of subjects administering UDCA at Day 0 will be ~~recruited~~.	7. For subjects being administered UDCA as part of their standard of care, the dose must have been stable for ≥3 months prior to, and including, Day 0 and must not have exceeded 20 mg/kg/day during this time. **Note 2**: **Subjects not taking UDCA at Day 0 must not have taken UDCA for ≥3 months prior to, and including, Day 0 and must not take UDCA during the DB period.** Subjects will be stratified according to UDCA use**,** and no more than 50% of subjects administering UDCA at Day 0 will be **enrolled**.
Synopsis Methodology, Inclusion Criteria and Section 8.2 Subject Inclusion Criteria	8. ~~For s~~ubjects being administered biologic treatments (eg, ~~A~~nti-TNF or anti-integrin monoclonal antibodies), immunosuppressants ~~or~~ systemic corticosteroids ~~they~~ must have been on a stable dose for ≥3 months prior to, and including, Day 0 and should plan to remain on a stable dose throughout the trial.	8. **S**ubjects being administered biologic treatments (eg, **a**nti-TNF or anti-integrin monoclonal antibodies), immunosuppressants**,** systemic corticosteroids**, or statins**, must have been on a stable dose for ≥3 months prior to, and including, Day 0 and should plan to remain on a stable dose throughout the trial.
Synopsis Methodology Inclusion Criteria and Section 8.2 Subject Inclusion Criteria	9. Contraception: female subjects of childbearing potential must use ≥1 effective method of contraception during the trial and until 4 weeks following the last dose of ~~IP~~ (including LTSE doses).	9. Contraception: female subjects of childbearing potential must use ≥1 effective method **(≤1% failure rate)** of contraception during the trial and until 4 weeks following the last dose of **investigational product** (including LTSE doses). **Effective methods of contraception are considered to be those listed below:**

Section	Original Text	Revised Text
		• **Double barrier method, ie, (a) condom (male or female) or (b) diaphragm, with spermicide; or** • **Intrauterine device; or** • **Vasectomy (partner), or** • **Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or** • **Abstinence, if in line with the preferred and usual lifestyle of the subject [where abstinence is defined as refraining from heterosexual intercourse during the trial duration (from first administration of investigational product until 4 weeks after the last dose of investigational product)]**
Synopsis Methodology Exclusion Criteria and Section 8.3 Subject Exclusion Criteria	4. Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including: • Current Child Pugh classification B or C • History of, or current diagnosis or suspicion of, cholangiocarcinoma or other hepatobiliary malignancy, or biliary tract dysplasia. • History of liver transplantation, ~~current placement on a liver transplant list,~~ or current model of end stage liver disease (MELD) score ≥12	5. Presence of clinical complications of chronic liver disease or clinically significant hepatic decompensation, including: • Current Child-Pugh classification B or C • History of, or current diagnosis or suspicion of, cholangiocarcinoma or other hepatobiliary malignancy, or biliary tract dysplasia. • History of liver transplantation, or current model of end stage liver disease (MELD) score ≥12

Section	Original Text	Revised Text
Synopsis Methodology Exclusion Criteria and Section 8.3 Subject Exclusion Criteria	5. Clinical evidence of dominant stricture (as evidenced by cholangiography or other appropriate imaging modality within the 12 months prior to Day 0)	5. Clinical evidence of dominant stricture (as evidenced by cholangiography or other appropriate imaging modality within the 12 months prior to Day 0) **or current biliary stent**
Synopsis Methodology Exclusion Criteria and Section 8.3 Subject Exclusion Criteria	9. History of other chronic liver diseases, including, but not limited to, primary biliary cirrhosis (PBC), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA) ~~and~~ hepatitis C virus	9. History of other chronic liver diseases, including, but not limited to, primary biliary cirrhosis (PBC), alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, hepatitis B virus (unless seroconverted and no positive Hepatitis B Virus DNA)**,** hepatitis C virus**, and overlap syndrome**
Synopsis Methodology Exclusion Criteria and Section 8.3 Subject Exclusion Criteria	12. Currently experiencing, or experienced within ≤1 month of Screening, ~~moderate to severe~~ pruritus requiring systemic or enteral treatment~~, or any history of severe pruritus~~	12. Currently experiencing, or experienced within ≤**3** month**s** of Screening, pruritus requiring systemic or enteral treatment.
Synopsis Methodology Exclusion Criteria and Section 8.3 Subject Exclusion Criteria	14. Administration of antibiotics is prohibited ≤1 month of Day 0.	14. Administration of antibiotics is prohibited ≤1 month of Day 0 **(unless subject is on a stable prophylaxis dose for at least 3 months prior to Day 0)**.

Section	Original Text	Revised Text
Synopsis Efficacy Analyses	~~An unblinded interim analysis for planning purposes will be conducted after approximately 50% of patients have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint: the change from Baseline in ALP, between OCA treatment groups (1.5 mg and 5 mg) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. No adjustments to the alpha level will be made.~~	*Text Moved to Synopsis Interim Analysis* **Interim Analysis** **An unblinded interim analysis for planning purposes will be conducted after approximately 50% of subjects have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint: the change from Baseline in ALP, between OCA treatment groups (1.5 mg and 5 mg) and placebo using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate. No adjustments to the alpha level will be made.**
List of Abbreviations and Definitions of Terms	~~IP investigational product~~	**RSI: Reference Safety Information** **SUSAR: suspected unexpected serious adverse reaction**

Section	Original Text	Revised Text
Section 5.3.2 Nonclinical Effects on Cholestasis	The results of trials performed in rodent models of cholestasis involving the administration of chemical agents that severely injure bile ducts (such as carbon tetrachloride [CCl_4] or lithocholic acid [LCA]) provide evidence that OCA is effective in preventing or reducing cholestasis *in vivo*. In the LCA model, co-infusion of OCA fully reversed the impairment of bile flow and protected against liver cell injury (Pellicciari 2002~~, Vairappan 2009~~). Results of other trials have demonstrated that OCA significantly reduces fibrotic collagen synthesis *in vitro* and in various rodent models of chronic liver injury that involve fibrosis and eventual cirrhosis, consistent with the progression of PSC (Albanis 2005, ~~Vairappan 2009~~).	The results of trials performed in rodent models of cholestasis involving the administration of chemical agents that severely injure bile ducts (such as carbon tetrachloride [CCl_4] or lithocholic acid [LCA]) provide evidence that OCA is effective in preventing or reducing cholestasis *in vivo*. In the LCA model, co-infusion of OCA fully reversed the impairment of bile flow and protected against liver cell injury (Pellicciari 2002). Results of other trials have demonstrated that OCA significantly reduces fibrotic collagen synthesis *in vitro* and in various rodent models of chronic liver injury that involve fibrosis and eventual cirrhosis, consistent with the progression of PSC (Albanis 2005, **Mookerjee 2015**).
Section 5.4 Clinical Experience with Obeticholic Acid	To date, OCA has been evaluated in the clinic in a total of ~~17~~ completed and ongoing trials, including patients with PBC and other chronic liver diseases (eg, portal hypertension and nonalcoholic steatohepatitis [NASH]) and healthy volunteers. Additional trials are also planned to further characterize the pharmacokinetic (PK) and pharmacodynamic~~s~~ (PD) properties of OCA as well as the safety and efficacy of OCA in subjects with PBC and other chronic liver diseases. As of 31 ~~Mar 2014~~, ~~1023~~ subjects have received at least one dose of OCA in completed or ongoing trials. ~~Of these, 414 (40%) were PBC subjects with exposure up to approximately 4.5 years~~. Overall, the PK profile of OCA is consistent with that expected of	To date, OCA has been evaluated in the clinic in a total of **25** completed and **8** ongoing trials, including patients with PBC and other chronic liver diseases (eg, portal hypertension and nonalcoholic steatohepatitis [NASH]) and healthy volunteers. Additional trials are also planned to further characterize the pharmacokinetic (PK) and pharmacodynamic (PD) properties of OCA as well as the safety and efficacy of OCA in subjects with PBC and other chronic liver diseases. As of 31 **Jan 2015**, **approximately 1650** subjects have received at least one dose of OCA in completed or ongoing trials. Overall, the PK profile of OCA is consistent with that expected of a bile acid. Phase 1 PK trials demonstrated that OCA was rapidly

Section	Original Text	Revised Text
	a bile acid. Phase 1 PK trials demonstrated that OCA was rapidly absorbed and extensively conjugated with glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates were 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 peaked shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.	absorbed and extensively conjugated with glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates were 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 peaked shortly after meals, consistent with gall bladder emptying into the duodenum as expected of a bile acid.
Section 5.5 Summary of Known Potential Risks with Investigational Product	Pruritus is a common symptom of chronic cholestatic diseases such as PBC and PSC. In subjects with PBC, treatment with OCA has been shown to cause a dose-dependent exacerbation of this common symptom and similar results can be expected in subjects with PSC. Pruritus has also been observed in clinical trials with OCA in other indications and in healthy volunteers, but at a lower frequency and at higher doses than that observed in subjects with chronic cholestasis. Investigator guidance for pruritus management strategies are outlined in Section 12.1.3.1 of the protocol. Other potential risks include liver toxicity, especially at higher doses of OCA, which is consistent with nonclinical findings and the chemical characteristics of OCA as a bile acid and detergent. An increase in liver function tests and hepat~~ic~~ AEs, including jaundice, were observed in subjects with PBC and NASH who were treated at doses that are several fold	**Investigators are referred to the current IB for a thorough presentation of the safety data associated with OCA. An overview is as follows:** Pruritus is a common symptom of chronic cholestatic diseases such as PBC and PSC. In subjects with PBC, treatment with OCA has been shown to cause a dose-dependent exacerbation of this common symptom and similar results can be expected in subjects with PSC. Pruritus has also been observed in clinical trials with OCA in other indications and in healthy volunteers, but at a lower frequency and at higher doses than that observed in subjects with chronic cholestasis. Investigator guidance for pruritus management strategies are outlined in Section 12.1.3.1 of the protocol. Other potential risks include liver toxicity, especially at higher doses of OCA, which is consistent with nonclinical findings and the chemical characteristics of OCA as a bile acid and detergent. An increase in

Section	Original Text	Revised Text
	higher (primarily 20 to 50 mg daily) than those studied in this protocol (1.5 mg, 3 mg, 5 mg, and 10 mg) doses. This is an important potential risk in subjects with PSC, where there is the possibility of dominant strictures of intra- and extra-hepatic bile ducts that could restrict bile flow. In order to monitor bile duct patency, the trial protocol requires that sites perform an ultrasound at the end of the DB phase and ~~thereafter~~ annually in the LTSE. Consistent with this potential risk, the present trial excludes subjects who have had, or who are suspected of having, a recent dominant stricture (Section 8.3). In addition, the trial calls for mandatory discontinuation of investigational product ~~(IP)~~ in those subjects whose liver chemistry (AST, ALT and or bilirubin) display clinically significant increases following the initiation of therapy (Section 8.4.1). The doses used in the present trial (1.5 mg to 10 mg) are amongst the lowest doses of OCA tested to date in a clinical setting. Lipoprotein changes have also been observed with OCA dosing in subjects with PBC (including a decrease in high density lipoprotein [HDL]). The clinical significance of these lipid findings remains unclear and is being studied further. Notably, despite an observed decrease in HDL levels, they generally remained within normal limits. The relevance of these findings to subjects with PSC is unclear and will be investigated further in this trial. ~~Investigators are referred to the current IB for a thorough presentation of the safety data associated with OCA.~~	liver function tests and hepat**obiliary** AEs, including jaundice, **ascites and acute cholecystitis** were observed in subjects with PBC and NASH who were treated at doses that are several fold higher (primarily 20 **mg** to 50 mg daily) than those studied in this protocol (1.5 mg, 3 mg, 5 mg, and 10 mg) doses. This is an important potential risk in subjects with PSC, where there is the possibility of dominant strictures of intra- and extra-hepatic bile ducts that could restrict bile flow. In order to monitor bile duct patency, the trial protocol requires that sites perform an ultrasound at **Screening, at** the end of the DB phase**,** and annually in the LTSE. Consistent with this potential risk, the present trial excludes subjects who have had, or who are suspected of having, a recent dominant stricture (Section 8.3). In addition, the trial calls for mandatory discontinuation of investigational product in those subjects whose liver chemistry (AST, ALT and or bilirubin) display clinically significant increases following the initiation of therapy (Section 8.4.1). The doses used in the present trial (1.5 mg to 10 mg) are amongst the lowest doses of OCA tested to date in a clinical setting. Lipoprotein changes have also been observed with OCA dosing in subjects with PBC (including a decrease in high-density lipoprotein [HDL]). The clinical significance of these lipid findings remains unclear and is being studied further. Notably, despite an observed decrease in HDL levels, they generally remained within normal limits. The relevance of

Section	Original Text	Revised Text
	In addition, the Data Safety Monitoring Committee (DSMC) will review safety data from the present trial as well as other ongoing OCA trials ~~on a periodic basis~~. Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability as noted in Section 7.4.3. ~~A few Sponsor representatives may be unblinded during the trial, as it is anticipated that this may speed a decision to make a dosing change in the study, if necessary. If there are any findings regarding safety, tolerability, or efficacy that indicate an alternative optimal LTSE starting dose, the starting dose in the LTSE may be reduced.~~	these findings to subjects with PSC is unclear and will be investigated further in this trial. In addition, the Data Safety Monitoring Committee (DSMC) will review safety data from the present trial as well as other ongoing OCA trials **at approximately quarterly intervals but at least every 6 months**. Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability as noted in Section 7.4.3.
Section 7.1 Overall Trial Design	*Long-Term Safety Extension Phase (LTSE)* Following completion of participation in the DB phase ~~at Week 24~~, subjects will ~~continue in the study in the open-label long-term safety extension (LTSE) phase for a further 24 months, and will~~ be ~~required at this time~~ to reconfirm their consent for participation in the ~~trial~~. The schedule of trial procedures for the LTSE is shown in Table 2. Upon a subject's completion of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA unless safety and tolerability warrant a dose reduction to 5 mg. The titration schedule and	*Long-Term Safety Extension Phase (LTSE)* Following completion of participation in the DB phase**,** subjects will be **asked** to reconfirm their consent for participation in the **LTSE phase (a further 24 months)**. The schedule of trial procedures for the LTSE is shown in Table 2. Upon a subject's completion of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in the DB phase with 10 mg OCA who will continue at 10 mg OCA unless safety and tolerability warrant a dose reduction to 5 mg. The titration schedule and options for the LTSE phase are detailed in Section 7.4.2. If an **I**nvestigator does not wish for a

Section	Original Text	Revised Text
	options for the LTSE phase are detailed in Section 7.4.2. If an ~~i~~nvestigator does not wish for a subject to be titrated in line with ~~the below schedule~~ this ~~should~~ be discussed with the ~~m~~edical ~~m~~onitor~~:~~ ~~A limited number of Sponsor representatives will remain unblinded during the DB phase of the study. If there are any findings regarding safety, tolerability, or efficacy that indicate an alternative optimal LTSE starting dose, the starting dose in the LTSE may be reduced.~~	subject to be titrated in line with Table 4**,** this **may** be discussed with the **M**edical **M**onitor**.**
Schedule of Trial Procedures, Table 1 Double-Blind Phase	Screening D0 Hepatic Ultrasound at W24 Dispense ~~IP~~ at D0, ~~W2, W6,~~ W12, ~~W14, W18,~~ W24 Serum Chemistry & Hematology *No Text* Footnote d: The Week 24 visit is the final visit during the DB treatment period. For subjects who continue into the LTSE, the Week 24 visit is also Day 1 of the LTSE.	Screening **(Day -30 to Day -1)** D**ay** 0[b] Hepatic Ultrasound at **Screening** and W24 Dispense **Investigational Product** at D**ay** 0,W12, W24 Serum Chemistry, Hematology**, & Coagulation Parameters** Footnote b: **Day 0 must occur by Day 31 for a subject to be eligible to continue in the trial.** Footnote d: The Week 24 visit is the final visit during the DB treatment period. For subjects who continue into the LTSE, the Week 24 visit is also Day 1 of the LTSE**, and unblinding occurs after the Week 24/LTSE Day 1 procedures have been completed (except dispensing of open-label investigational product).**

Section	Original Text	Revised Text
	Footnote ~~g~~: Height is measured ~~only~~ at the Screening ~~V~~visit.	Footnote **h**: Height is measured at the Screening **v**isit **only**.
	Footnote ~~i~~: TE: at trial sites where the Fibroscan® TE device is available.	Footnote j: TE: at trial sites where the Fibroscan® TE device is available. **TE has a 5-day visit window. For the Day 0 assessment, TE should occur either on Day 0 or within 5 days prior to Day 0. For the Week 24 assessment, the TE should occur within ±5 days of the onsite visit if it is not possible to schedule the TE on the same day as that visit, but the visit(s) should remain within the overall visit window.**
	No Text	**Footnote k: Hepatic ultrasound has a ±5-day visit window (ie, if it is not possible to schedule the ultrasound on the same day as the onsite visit, it may occur within 5 days on either side of the visit, but the visit(s) should remain within the overall visit window).**
	Footnote ~~k~~: Subjects with UC ~~and CD~~ will be asked to complete a diary recording details ~~of their symptoms~~ in the 7 days prior to their next scheduled visit~~.~~	Footnote **m**: Subjects with UC will be asked to complete a diary **the day prior to their next trial visit,** recording details **since their last scheduled visit. Subjects with CD should complete the diary** in the 7 days prior to their next clinic visit**. Diary card data from the Screening period are collected at the Day 0 visit.**
	Footnote ~~m~~: Questionnaire completed ~~with input from~~ the subject.	Footnote **o**: Questionnaire completed **by** the subject. Footnote r: Investigational product is dispensed only for subjects who continue into the LTSE.

Section	Original Text	Revised Text
	Footnote r: Investigational product is dispensed only for subjects who continue into the LTSE.	**(Dispensing of open-label investigational product occurs after completion of the Week 24/LTSE Day 1 procedures and the subsequent unblinding of the subject's treatment allocation.)**
Schedule of Trial Procedures, Table 2 LTSE Phase	*No Text*	**Contact Wk2 ±3d – Safety Contact**
	Serum Chemistry & Hematology	Serum Chemistry, Hematology**, & Coagulation Parameters**
	Footnote c: The LTSE D1 is also the final visit (Week 24) of the DB treatment period.	Footnote c: The LTSE D1 is also the final visit (Week 24) of the DB treatment period. **For subjects continuing into the LTSE, unblinding occurs after the Week 24/LTSE Day 1 procedures have been completed (except dispensing of open-label investigational product).**
	No Text	Footnote g: **The Safety Contact can be either via telephone or email, and does not require an onsite visit.**
	Footnote ~~h~~: TE: at trial sites where the Fibroscan® TE device is available.	Footnote **i**: TE: at trial sites where the Fibroscan® TE device is available. **The TE should occur within ±5 days of the onsite visit if it is not possible to schedule the TE on the same day as that visit, but the visit(s) should remain within the overall visit window.**
	No Text	Footnote j: **Hepatic ultrasound has a ±5-day visit window (ie, if it is not possible to schedule the ultrasound on the same day as the onsite visit, it may occur within 5 days on either side of the visit, but the visit(s) should remain within the overall visit window).**

Section	Original Text	Revised Text
	Footnote ~~j~~: Subjects with UC ~~and CD~~ will be asked to complete a diary recording details of their symptoms in the 7 days prior to their next scheduled visit. Footnote ~~l~~: Questionnaire completed ~~with input from~~ the subject. *No Text*	Footnote **l**: **Subjects with UC will be asked to complete a diary the day prior to their next trial visit, recording details since their last scheduled visit. Subjects with CD should complete the diary** in the 7 days prior to their next clinic visit**.** Footnote **n**: Questionnaire completed **by** the subject. Footnote o: **Investigational product is dispensed only for subjects who continue into the LTSE. (Dispensing of open-label investigational product occurs after completion of the Week 24/LTSE Day 1 procedures and the subsequent unblinding of the subject's treatment allocation.)**
Section 7.4.2 LTSE Phase	Upon a subject's completion of the Week 24 visit, at the end of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in DB with 10 mg OCA who will continue at 10 mg OCA (Table 4) unless safety and tolerability warrant a dose reduction to 5 mg. ~~If an investigator does not wish for a subject to be titrated in line with the below schedule this should be discussed with the medical monitor:~~ During the LTSE~~,~~ phase subjects may titrate to higher doses of OCA, at a frequency not greater than 3 monthly (ie, at each of the scheduled visits), up to a maximum dose of 10 mg daily. The guideline for an increase in the dose of open-label OCA is based on the goal of achieving ALP <1.5x ULN and	Upon a subject's completion of the Week 24 visit, at the end of the DB phase, the trial blind will be broken in order to assign the starting OCA dose for the LTSE phase. It is intended that subjects will commence treatment at 5 mg OCA, except those subjects who completed treatment in **the** DB **phase** with 10 mg OCA who will continue at 10 mg OCA (Table 4) unless safety and tolerability warrant a dose reduction to 5 mg. **If an Investigator does not wish for a subject to be titrated in line with the above schedules, this may be discussed with the Medical Monitor.** During the LTSE phase subjects may titrate to higher doses of OCA, at a frequency not greater than 3 monthly (ie, at each of the scheduled visits), up to a maximum dose of 10 mg daily. The guideline for an

Section	Original Text	Revised Text
	tolerability. ~~Subjects may be titrated in the order~~ 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg ~~unless otherwise clinically indicated~~. ~~An increase in the dose of OCA may occur at intervals no more frequent than once per month.~~	increase in the dose of open-label OCA is based on the goal of achieving ALP <1.5x ULN and tolerability. **Doses of OCA should** be titrated **as follows, unless clinically indicated:** 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to10 mg.
Section 7.4.3 Safety Criteria for Adjustment or Stopping Doses	~~The~~ Data Safety Monitoring Committee (DSMC) will review safety data from ~~the present~~ trial as well as other ongoing OCA trials ~~on a periodic basis.~~ Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability. At a minimum, the occurrence of ~~two~~ life threatening serious adverse events (SAEs) or an SAE resulting in death will trigger an unscheduled and unblinded review of the data by the DSMC to determine if the trial should continue. Section 7.5 details the criteria for trial termination. Reasons for discontinuation of individual subjects are noted in Section 8.4.1 and Section 8.4.2.	**An independant** Data Safety Monitoring Committee (DSMC) will review safety data from **this** trial as well as other ongoing OCA trials **at approximately quarterly intervals but at least every 6 months.** Adjustments to or stopping of the protocol-defined doses may be considered based on DSMC evaluation of OCA safety and tolerability. At a minimum, the occurrence of **2** life threatening serious adverse events (SAEs) or an SAE resulting in death will trigger an unscheduled and unblinded review of the data by the DSMC to determine if the trial should continue. Section 7.5 details the criteria for trial termination. Reasons for discontinuation of individual subjects are noted in Section 8.4.1 and Section 8.4.2.
Section 7.5 Criteria for Trial Termination	The Sponsor reserves the right to terminate the trial at any time.	The Sponsor reserves the right to terminate the trial at any time. **Additionally, it is agreed that, for reasonable cause, the Investigator may terminate the trial at his/her site at any time.**
Section 8.4.2 Other Reasons for Study Discontinuation	**Other Reasons ~~for Trial or Treatment Discontinuation or Potential Discontinuation of Subjects~~** ~~A reasonable effort must be made to determine the reason(s) why a subject fails to return for final visit or~~	**Other Reasons for Study Discontinuation** **A subject should be discontinued from the study if:**

Section	Original Text	Revised Text
	~~is discontinued from the trial. This information and date must be recorded on the appropriate case report form (CRF). The following events are considered appropriate (potential) reasons for a subject to discontinue from the trial:~~ • The subject decides that it is in his/her best interest. It is fully understood that all subjects volunteer for the trial and that they may withdraw their consent to continue in the trial at any time. • The ~~i~~investigator considers that it is advisable or in the best interest of the subject • There is a major violation of the clinical trial protocol for the subject • Noncompliance of the subject • The development of any exclusion criteria (see Section 8.3) • ~~An inability to~~ provide blood or urine samples • The occurrence of clinical or laboratory AEs considered by the ~~i~~investigator to be clinically important	• The subject decides that it is in his/her best interest. It is fully understood that all subjects volunteer for the trial and that they may withdraw their consent to continue in the trial at any time. • The **I**nvestigator considers that it is advisable or in the best interest of the subject**.** • There is a major violation of the clinical trial protocol for the subject **that would jeopardize the subject's safety and/or data quality.** • **There is significant n**oncompliance of the subject **that would jeopardize the subject's safety and/or data quality.** • The development of any exclusion criteria (see Section 8.3) **that would jeopardize the subject's safety and/or data quality.** • **The subject is consistently unable to** provide blood or urine samples**.** • The**re is an** occurrence of clinical or laboratory AEs considered by the **I**nvestigator to be clinically important**, such that they would jeopardize the subject's safety.** **A reasonable effort must be made to determine the reason(s) why a subject fails to return for his/her final visit or is discontinued from the trial.**

Section	Original Text	Revised Text
		This information and date must be recorded on the appropriate case report form (CRF).
Section 8.4.2 Other Reasons for Study Discontinuation, Bacterial Cholangitis	~~Subjects should temporarily interrupt treatment with IP and receive standard of care treatment~~. Discontinuation from the trial is not mandatory in cases of bacterial cholangitis unless signs and symptoms do not resolve within a clinically reasonable timeframe (typically within 1 month or as agreed upon with the ~~m~~edical ~~m~~onitor) or the cholangitis becomes life threatening in the opinion of the ~~i~~nvestigator or ~~m~~edical ~~m~~onitor. In any event, ~~IP~~ should not be restarted until signs and symptoms have resolved and the subject's liver biochemistry has returned to pre-cholangitis levels.	**Investigational product may be interrupted at the discretion of the Investigator.** Discontinuation from the trial is not mandatory in cases of bacterial cholangitis unless signs and symptoms do not resolve within a clinically reasonable timeframe (typically within 1 month or as agreed upon with the **M**edical **M**onitor) or the cholangitis becomes life-threatening in the opinion of the **I**nvestigator or **M**edical **M**onitor. In any event, **investigational product** should not be restarted until signs and symptoms have resolved and the subject's liver biochemistry has returned to pre-cholangitis levels.
Section 8.4.2 Other Reasons for Study Discontinuation, Bile Duct Stricture and Pruritus	**Bile Duct Stricture** ~~IP should~~ be interrupted if a subject develops a stricture requiring intervention (eg, drainage, ERCP, stent) in order to re-establish bile flow. ~~The medical monitor should be contacted to confirm the subject's eligibility to continue in the trial. Lack of improvement (or worsening)~~ within 1 month of treatment ~~will require~~ further evaluation by the ~~i~~nvestigator and discussion and agreement with the ~~m~~edical ~~m~~onitor before a subject is considered eligible to resume ~~IP~~ administration or to continue in the trial. ~~It is agreed that, for reasonable cause, the investigator may terminate the trial at his/her site or the Sponsor may decide to terminate the trial.~~	**Bile Duct Stricture** **Investigational product may** be interrupted **at the discretion of the Investigator** if a subject develops a stricture requiring intervention (eg, drainage, ERCP, stent) in order to re-establish bile flow. **If the investigational product has been interrupted and the subject does not show improvement** within 1 month of treatment**,** further evaluation by the **I**nvestigator and discussion and agreement with the **M**edical **M**onitor **is required** before a subject is considered eligible to resume **investigational product** administration or to continue in the trial. **Pruritus** **Pruritus is a common symptom in PBC but less common in PSC (Chapman 2011). Investigator**

Section	Original Text	Revised Text
		guidance for pruritus management strategies are outlined in Section 12.1.3.1 of this protocol. Subjects who experience one or more episodes of severe pruritus that are not tolerable based on Investigator assessment, despite optimal supportive treatment as outlined in Section 12.1.3.1, should be discontinued from the trial.
Section 9.1 Investigational Product Treatment Regimen	~~IP~~ will be dispensed in bottles of 100 tablets, and subjects will be instructed to take the number of tablets indicated by their treatment group. During the first 12 weeks of the DB phase, subjects will be instructed to administer ~~two~~ tablets daily: one 1.5 mg (small) tablet and one 5 mg (big) tablet.	**Investigational product** will be dispensed in bottles of 100 tablets, and subjects will be instructed to take the number of tablets indicated by their treatment group. During the first 12 weeks of the DB phase, subjects will be instructed to administer **2** tablets daily **with water**: one 1.5 mg (small) tablet and one 5 mg (big) tablet.
Section 9.2 Concomitant Medications	Relevant information about all concomitant drugs (including prescribed, over the counter, or herbal preparations) taken prior to (ie, within 30 days of ~~Day 0~~) and during the trial must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the trial.	Relevant information about all concomitant drugs (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of **Screening**) and during the trial must be recorded in the source documents and CRF, as well as any dose or dose regimen changes that occur during the trial.
Section 9.2.1 Ursodeoxycholic Acid	Subjects taking UDCA at Day 0 should maintain this dose and the timing of administration of UDCA for the duration of the DB phase of the trial (24 weeks). Subjects who ~~were unable to tolerate~~ UDCA ~~prior to participating in~~ the trial should not initiate UDCA therapy at any time during their participation in the DB phase of trial.	Subjects taking UDCA at Day 0 should maintain this dose and the timing of administration of UDCA for the duration of the DB phase of the trial (24 weeks). Subjects who **are not taking** UDCA **on entry into** the trial should not initiate UDCA therapy at any time during their participation in the DB phase of **the** trial.

Section	Original Text	Revised Text
Section 9.2.3 Prohibited Medications	• Systemic or enteral therapy for pruritus in the month prior to Screening. A subject may remain in the study if they require systemic or enteral therapy for pruritus after the initiation of investigational product administration • Administration of antibiotics within 1 month of Day 0, except if administered for acute cholangitis whereby its use is prohibited within 3 months of Day 0. Subjects being administered the following medications at Day 0 may enter the trial provided they have been on a stable dose for ≥3 months prior to, and including, ~~Screening~~ and remain on a stable dose throughout the trial: • Anti-TNF and anti-integrin antibodies • Immunosuppressants (eg, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline) • Corticosteroids	• Systemic or enteral therapy for pruritus in the **3** month**s** prior to Screening. A subject may remain in the study if they require systemic or enteral therapy for pruritus after the initiation of investigational product administration**.** • Administration of antibiotics within 1 month of Day 0 **(unless subject is on a stable prophylaxis dose for at least 3 months prior to Day 0)**, except if administered for acute cholangitis whereby its use is prohibited within 3 months of Day 0. Subjects being administered the following medications at Day 0 may enter the trial provided they have been on a stable dose for ≥3 months prior to, and including, **Day 0** and remain on a stable dose throughout the trial: • Anti-TNF and anti-integrin antibodies • Immunosuppressants (eg, azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline) • Corticosteroids • **Statins**

Section	Original Text	Revised Text
Section 9.4 Randomization and Blinding	~~A limited number of Sponsor representatives will remain unblinded to the treatment allocation during the DB phase, for example, to enable evaluation of safety and tolerability. This will not affect the scientific integrity of the study or data.~~	*No Text*
Section 9.4.2 Unblinding Procedures – Emergency Unblinding	*No Text*	**9.4.2 Unblinding Procedures – Emergency Unblinding** **For the DB phase of the trial, treatment assignment will be made available to the Investigator for emergency use only through the IWRS. 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 accidental unblinding or unblinding due to 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 the purpose of evaluating an emergent safety issue, the Medical Monitor will document within trial documentation the rationale, circumstances, and**

Section	Original Text	Revised Text
		the person or persons being informed about the unblinding. **The DSMC (refer to Section 13.6.2) will have access to the IWRS and will be able to unblind individual subjects. Refer to Section 13.6.2 for further details regarding DSMC access to blinded and unblinded data. The DSMC will document, 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), details about any unblinded subject data reviews. Cases of premature unblinding (as noted above) will be reviewed by the DSMC.** **Access to treatment assignments will also be made available through the IWRS to the appropriate, named individual(s) responsible for reporting SAEs and suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities.**
Section 9.6.1 Visit Windows	All trial visits during the DB period are relative to Day 0 (eg, if the Week 6 visit occurs 4 days late, the Week 12 visit should still be 12 weeks from Day 0). The Screening visit should occur ≤30 days prior to the Day 0 visit. All visits during the DB treatment period should occur within ± 1 week of the indicated time. The exception to this is the Week 2 visit, which should occur within ± 3 days of the indicated time. During the LTSE period, visits are relative to LTSE Day 1 (which is also the DB Week 24 visit) and all visits during this period should occur within	All trial visits during the DB period are relative to Day 0 (eg, if the Week 6 visit occurs 4 days late, the Week 12 visit should still be 12 weeks from Day 0). The Screening visit should occur ≤30 days **(ie, Day -30 to Day -1)** prior to the Day 0 visit. All visits during the DB treatment period should occur within ±1 week of the indicated time. The exception to this is the Week 2 visit, which should occur within ±3 days of the indicated time. During the LTSE period, visits are relative to LTSE Day 1 (which is also the DB Week 24 visit) and all

Section	Original Text	Revised Text
	± 2 weeks of the indicated time, except for the Follow-Up visit, which should occur within ± 1 week.	visits during this period should occur within ±2 weeks of the indicated time, except for the **Week 2 Safety Contact which should occur within ±3 days and the** Follow-Up visit, which should occur within ±1 week.
Section 9.6.3 Screening Procedures (Within 30 Days of Day 0)	The Screening ~~V~~visit assessments must be performed within ≤30 days prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria.	The Screening **v**isit assessments must be performed within ≤30 days **(ie, Day -30 to Day -1)** prior to Day 0 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria.
Section 9.6.3 Screening Procedures (Within 30 Days of Day 0)	Screening ~~V~~visit procedures are as follows: • The subject is to review the PIS and sign the ICF. Written informed consent must be obtained from the subject before performing any trial related procedures, including Screening procedures. (Note: Collection of AEs commences from the point the subject signs the consent form.) • Assign subject number • Collect medical history • Record prior (within 30 days of ~~Day 0~~) and current concomitant medications • Verify inclusion and exclusion criteria for eligibility • Perform a physical examination, including height ~~(Screening Visit only)~~ and weight. See Section 12.2.2 for physical examination requirements.	Screening **v**isit procedures are as follows: • The subject is to review the PIS and sign the ICF. Written informed consent must be obtained from the subject before performing any trial related procedures, including Screening procedures. (Note: Collection of AEs commences from the point the subject signs the consent form.) • Assign subject number**.** • Collect medical history**.** • Record prior (within 30 days of **Screening**) and current concomitant medications**.** • Verify inclusion and exclusion criteria for eligibility**.** • Perform a physical examination, including height and weight. See Section 12.2.2 for physical examination requirements.

Section	Original Text	Revised Text
	• Record vital signs • Perform a standard 12-lead electrocardiogram (ECG) • For subjects with UC: provide the diary and request subject completes this ~~for each of the 7 consecutive days prior to the next scheduled~~ visit. • For subjects with CD: provide the diary and request subject completes this for each of the 7 consecutive days prior to the ~~next scheduled~~ visit. • Obtain blood samples for serum chemistry and hematology **Note**: If a subject has an ALP value ~~≤~~2x ULN, a further sample may be taken during the Screening period (at least 14 days after the initial sample was taken), and provided the mean ALP is ≥2x ULN, the subject will have met inclusion criterion 4 (ALP at Screening ≥2x ULN)	• Record vital signs**.** • Perform a standard 12-lead electrocardiogram (ECG)**.** • **Perform hepatic ultrasound to assess bile duct patency.** • For subjects with UC: provide the diary and request subject completes this **the day prior to the Day 0 visit, to reflect their symptoms since the Screening** visit. • For subjects with CD: provide the diary and request subject completes this for each of the 7 consecutive days prior to the **Day 0** visit. • Obtain blood samples for serum chemistry, hematology**, and coagulation.** **Note**: If a subject has an ALP value <2x ULN, a further sample may be taken during the Screening period (at least 14 days after the initial sample was taken), and provided the mean ALP is ≥2x ULN, the subject will have met inclusion criterion 4 (ALP at Screening ≥2x ULN)**.**

Section	Original Text	Revised Text
Section 9.6.4 Day 0 Procedures, Bullets 5, 6 & 15	• For subjects with UC: obtain partial Mayo score (excluding endoscopy). See Appendix B for details. • For subjects with CD: complete CDAI assessments ~~and assign CDAI score~~. See Appendix F for details. • Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.	• For subjects with UC: obtain partial Mayo score (excluding endoscopy) **using the data from the diary card provided at the Screening visit**. See Appendix B for details. • For subjects with CD: complete CDAI assessments **using the data from the diary card provided at the Screening visit**. See Appendix F for details. • Subjects with UC or CD: provide the **appropriate** diary **card** and request this is completed for **the** 7 consecutive days prior to their next scheduled visit **(for subjects with CD) and the day prior to their next scheduled visit (for UC subjects)**.
Sections 9.6.4–9.6.12, Sections 9.6.16–9.6.19, 9.6.21–9.6.22 Visit Procedures	• Obtain blood samples for serum chemistry~~and~~ hematology	• Obtain blood samples for serum chemistry, hematology**, and coagulation**
Sections 9.6.5, 9.6.6, 9.6.7, 9.6.8, 9.6.9 Visit Procedures	• Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.	• Subjects with UC or CD: provide the **appropriate** diary **card** and request this is completed for **the** 7 consecutive days prior to their next scheduled visit **(for subjects with CD) and the day prior to their next scheduled visit (for UC subjects)**.

Section	Original Text	Revised Text
Sections 9.6.5, 9.6.6, 9.6.8, 9.6.9 Visit Procedures	• Record the visit in IWRS ~~and dispense indicated bottles of IP~~	• Record the visit in IWRS
Section 9.6.7 Week 12 (Titration Visit) Procedures	• For sites and subjects participating in PK sampling: obtain samples for PK analysis (see Section 11.5 for sampling schedule)	• For sites and subjects participating in PK sampling: obtain samples for PK analysis (see Section 11.5 for sampling schedule). **Subjects undergoing PK sampling should take the currently assigned dose (ie, lower dose); the titrated dose should be taken by the subject the following day.**
Section 9.6.10 Week 24/LTSE Day 1 Procedures; Subjects Participating in the LTSE	• Unblind the subject's treatment allocation in IWRS (as detailed in ~~the study reference manual)~~ and document the dose of OCA on which the subject will commence the LTSE.	• Unblind the subject's treatment allocation in IWRS (as detailed in **a separate trial document**) and document the dose of OCA on which the subject will commence the LTSE.
Sections 9.6.10, 9.6.11, 9.6.16, 9.6.17, 9.6.18, 9.6.19, 9.6.20, 9.6.21 Visit Procedures	• Subjects with UC or CD: provide the diary and request this is completed for 7 consecutive days prior to their next scheduled visit.	• Subjects with UC or CD: provide the **appropriate** diary **card** and request this is completed for **the** 7 consecutive days prior to their next scheduled visit **(for subjects with CD) and the day prior to their next scheduled visit (for UC subjects)**.

Section	Original Text	Revised Text
Section 9.6.15 LTSE Week 2 Procedures	*No Text*	**9.6.15 LTSE Week 2 Procedures** **The subject will be contacted by the study site staff 2 weeks after the start of the LTSE phase to assess safety.**
Sections 9.6.20, 9.6.21 Visit Procedures	• Obtain blood samples for: – Serum chemistry and hematology – FGF-19 – CRP – ELF markers and other analytes – Plasma bile acids and C4 ~~– Apolipoprotein and NMR lipoprotein panel~~ – Genetics study (if subject has consented to provide a sample for RNA analysis)	• Obtain blood samples for: – Serum chemistry**,** hematology**, and coagulation** – FGF-19 – CRP – ELF markers and other analytes – Plasma bile acids and C4 – Genetics study (if subject has consented to provide a sample for RNA analysis)
Section 9.6.22 Follow-Up Visit: LTSE	• Obtain blood samples for: – Serum chemistry and hematology – ~~Apolipoprotein and NMR lipoprotein panel~~	• Obtain blood samples for: – Serum chemistry and hematology

Section	Original Text	Revised Text
Section 10.4 Investigational Product Administration	Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1). ~~IP~~ administration should occur at approximately the same time of day throughout the duration of the trial. Subjects must be instructed to swallow the indicated number of tablets whole; they must not chew, divide, or crush the tablets.	Subjects will be instructed to begin dosing on the day after the Day 0 visit (ie, on Day 1). **Investigational product** administration should occur at approximately the same time of day throughout the duration of the trial. Subjects must be instructed to swallow the indicated number of tablets whole **with water**; they must not chew, divide, or crush the tablets.
Section 10.4.1 Investigational Product Dispensation	~~At subsequent clinic visits, IP will be dispensed after confirmation of continued subject compliance and eligibility.~~ At the 12 Week ~~V~~visit during the DB phase of the clinical study, subjects will receive 4 bottles of ~~IP (see Table 6)~~.	At the 12 Week **v**isit during the DB phase of the clinical study, subjects will receive 4 bottles of **investigational product**.
Section 10.4.3 Overdose	The maximum dose of OCA that has been given to humans is 500 mg as a single dose and 250 mg as a multiple dose. Reversible increases in aminotransferases were seen in most of the healthy volunteers who took 250 mg OCA. If overdose occurs in a subject enrolled in the trial, general medical supportive measures should be provided, including observation and follow-up (eg, serum chemistry) as appropriate. Due to the extensive enterohepatic recirculation of OCA it is likely that it will take several days before blood (and organ) concentrations of the drug will decrease. Treatment with cholestyramine (eg, Questran™), colesevelam (eg, Welcol™) and other BAS is recommended given that they should bind and eliminate the drug in feces.	The maximum dose of OCA that has been given to humans is 500 mg as a single dose and 250 mg as a multiple dose. Reversible increases in aminotransferases were seen in most of the healthy volunteers who took 250 mg OCA. If overdose occurs in a subject enrolled in the trial, general medical supportive measures should be provided, including observation and follow-up (eg, serum chemistry) as appropriate. Due to the extensive enterohepatic recirculation of OCA it is likely that it will take several days before blood (and organ) concentrations of the drug will decrease. Treatment with cholestyramine (eg, Questran™), colesevelam (eg, Welcol™) and other BAS is recommended given that they should bind and eliminate the drug in feces. The **Sponsor** should be notified immediately in the

Section	Original Text	Revised Text
	The ~~Medical Monitor~~ should be notified immediately in the event of a significant overdose.	event of a significant overdose.
Section 11.3 Secondary Assessments	Disease-Specific Symptoms To assist sites with recording and calculating the partial Mayo score and the CDAI ~~subjects with UC and CD, respectively, will be asked to complete a diary in the 7 days prior to their next scheduled trial visit to record their relevant symptoms~~. The PI will transcribe relevant information into the subject's medical records for SDV and retain the diary cards. Pertinent aspects of these data will be recorded in the CRF.	Disease-Specific Symptoms To assist sites with recording and calculating the partial Mayo score and the CDAI**, subjects with UC will be asked to complete a diary the day prior to the next scheduled visit, recording details since their last visit; and subjects with CD should complete the diary in the 7 days prior to their next clinic visit.** The PI will transcribe relevant information into the subject's medical records for SDV and retain the diary cards. Pertinent aspects of these data will be recorded in the CRF. **Data from the Screening period diary card will be recorded at Day 0.**
Section 11.5 Pharmacokinetics and Bile Acid Assessments	Following collection of the fasted laboratory samples (8 hour overnight fast) at Week 12 and Week 24 (as noted in Table 1), subjects who are participating in the PK/bile acid assessment will each receive a single dose of their allocated ~~IP~~ 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. The trial specific laboratory manual will include details of the volume of blood required to be drawn during each sampling timepoint as well as other logistical details and sample handling	Following collection of the fasted laboratory samples (8 hour overnight fast) at Week 12 and Week 24 (as noted in Table 1), subjects who are participating in the PK/bile acid assessment will each receive a single dose of their allocated **investigational product** with approximately 240 mL of water. **At Week 12, subjects will receive their dose assigned prior to titration (ie, the lower dose of investigational product).** 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. The trial-specific laboratory manual will include details of the volume of blood required to be drawn during each sampling timepoint as well as other logistical details and

Section	Original Text	Revised Text
	requirements. Subjects should not drink additional water for 1 hour after taking the dose of ~~IP~~. After approximately 1 hour post-dose, subjects will be fed a ~~standardized~~ meal ~~consisting of a Nutridrink™ (Nutricia)~~.	sample handling requirements. Subjects should not drink additional water for 1 hour after taking the dose of **investigational product**. After approximately 1 hour postdose, subjects will be fed a meal **replacement drink**.
Section 12.1.3.1 Severity of Pruritus	Pruritus was the most common AE seen in the Phase 2 and Phase 3 PBC trials and thus may occur in this trial. Subjects experiencing, or who have experienced within ≤1 month of Screening, ~~moderate to severe~~ pruritus requiring systemic or enteral treatment~~, or any history of severe pruritus (as defined in Table 9)~~ are excluded from participating this trial.	Pruritus was the most common AE seen in the Phase 2 and Phase 3 PBC trials and thus may occur in this trial. Subjects experiencing, or who have experienced within ≤**3** month**s** of Screening, pruritus requiring systemic or enteral treatment are excluded from participating **in** this trial.
Section 12.1.4.2 Reporting of SAEs	In agreeing to the provisions of this protocol, the ~~i~~nvestigator accepts all legal responsibilities for immediate reporting of SAEs to the ~~medical monitor~~. ~~The medical monitor for this trial is:~~ ~~Roya Hooshmand-Rad, MD, PhD~~ ~~Telephone: +1 858-964-1571 (Pacific time zone)~~ ~~Mobile: +1 858-880-6485 (Pacific time zone)~~ ~~Email: rhooshmand-rad@interceptpharma.com~~ ~~SAE Fax: + 1 800-497 8521~~ ~~SAE Email: **sae@interceptpharma.com**~~ All SAEs 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	In agreeing to the provisions of this protocol, the **I**nvestigator 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.** SAEs are reported by entering the SAE data into the **study specific** EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by**:** • **E-mail to the SAE email address: sae@interceptpharma.com** • **Fax using a paper SAE report form: +1 800 497 8521** • **Telephone: +1 844 250 6398**

Section	Original Text	Revised Text
	the EDC system will automatically notify the ~~medical monitor~~ of the event. In the event that the EDC system is inaccessible, an SAE may 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 ~~i~~nvestigator will assess whether the event is causally related to the ~~IP~~. The Sponsor, ~~Intercept,~~ will also assess whether the event is causally related to the ~~IP~~ in addition to assessing the overall safety profile of the ~~IP~~. The Sponsor will notify the appropriate regulatory agencies as well as all participating ~~i~~nvestigators of investigational new drug (IND) ~~s~~afety ~~r~~eports/~~e~~xpedited ~~s~~afety ~~r~~eports	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 **I**nvestigator 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 **I**nvestigators of investigational new drug (IND) **S**afety **R**eports/**E**xpedited **S**afety **R**eports that occur during the trial within the time frames required by each regulatory agency. **An SAE assessed with possible, probable, or definite causal relationship to the investigational product and unexpected according to the IB Reference Safety Information (RSI), is known as a suspected unexpected serious adverse reaction (SUSAR).**

Section	Original Text	Revised Text
	that occur during the trial within the time frames required by each regulatory agency. The ~~i~~nvestigator is responsible for submitting ~~information on IND s~~afety ~~r~~eports/~~e~~xpedited ~~s~~afety ~~r~~eports received from the Sponsor to her/his local IRB/IEC. Documentation of the submissions to IRBs/IEC and health authorities must be retained in the appropriate trial file(s). As instructed by the Sponsor, ~~IND s~~afety ~~r~~eports/~~e~~xpedited ~~s~~afety ~~r~~eports should be retained ~~with the current~~ IB.	**The Investigator must report SUSARs using the SAE reporting method described above.** **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 **I**nvestigator is responsible for submitting **S**afety **R**eports/**E**xpedited **S**afety **R**eports received from the Sponsor to her/his local IRB/IEC**, in compliance with the local country requirements**. **For the European Union, the Sponsor will notify the regulatory agencies and report SUSARs via the Eudra Vigilance database within 7 calendar days of a SUSAR involving death or a life-threatening SUSAR, and all other SUSARs within 15 calendar days.** Documentation of the submissions to IRBs/IEC**s** and health authorities **(as applicable)** must be retained in the appropriate trial file(s). As instructed by the Sponsor, **S**afety **R**eports/**E**xpedited **S**afety **R**eports should be retained **in the appropriate Investigator site trial files, or with the** IB.
Section 12.1.5 Anticipated Serious Adverse Events Associated with PSC	There are a number of events which are commonly associated with PSC and for the Sponsor's Regulatory reporting purposes, these events are considered to be 'Expected' in this patient population and are listed ~~below~~.	There are a number of events which are commonly associated with PSC and for the Sponsor's Regulatory reporting purposes, these events are considered to be 'Expected' in this patient population and are listed **in the IB**.

Section	Original Text	Revised Text
Section 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 trial. The ~~i~~nvestigator should comply with requests by the ~~m~~edical ~~m~~onitor 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 ~~i~~nvestigator should provide input into the SAE narrative and provide timely information to ensure prompt follow up and closure of the SAE report.	The safety data recorded in the CRF represent the official record of all AEs and SAEs reported in the trial. The **I**nvestigator should comply with requests by the **M**edical **M**onitor 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 **Sponsor**, the **I**nvestigator should provide input into the SAE narrative and provide timely information to ensure prompt follow**-**up and closure of the SAE report.
Section 12.1.7 Notification of Post-Trial SAEs	If an ~~i~~nvestigator becomes aware of an SAE that may be attributable to the ~~IP~~ at any time after the end of the trial, the ~~medical monitor~~ should be notified immediately (ie, within 24 hours).	If an **I**nvestigator becomes aware of an SAE that may be attributable to the **investigational product** at any time after the end of the trial, the **Sponsor** should be notified immediately (ie, within 24 hours).
Section 12.1.8 Follow-Up of AEs and SAEs	*No Text*	**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.**

Section	Original Text	Revised Text
Section 12.2.5 Laboratory Assessments	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 test-article 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 trial.~~ 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 until pregnancy outcome.	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 test-article related AE, is identified; or until further follow-up is deemed medically unnecessary. Urine based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits. **Additionally, in accordance with local country or site requirements, additional urine pregnancy tests may be performed.** 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 until pregnancy outcome.
Section 13.6.1 Interim Analysis	An unblinded interim analysis will be conducted after approximately 50% of subjects have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint, the change from Baseline in ALP, between OCA treatment groups and placebo. No adjustments to the alpha level will be made.	An unblinded interim analysis will be conducted after approximately 50% of subjects have completed the initial 12-weeks of blinded treatment. The trial will not be terminated early for futility. The interim analysis will compare at Week 12, the same variable as will be analyzed for the primary endpoint, the change from Baseline in ALP, between OCA treatment groups **(1.5 mg and 5 mg)** and placebo **using an analysis of covariance (ANCOVA) model with fixed effects for treatment group and randomization strata and Baseline as a covariate**. No adjustments to the alpha level will be made.

Section	Original Text	Revised Text
Section 13.6.2 Data and Safety Monitoring Committee	An independent DSMC will review safety data ~~at periodic intervals~~ from this trial. The DSMC includes internationally recognized hepatologists, pharmaceutical physicians and statistician(s). 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 ~~i~~nvestigators in this trial 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 trial.	An independent DSMC will review safety data from this trial**, as well as other ongoing OCA trials at approximately quarterly intervals, but at least every 6 months**. The DSMC includes internationally recognized hepatologists, pharmaceutical physicians and statistician(s). 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 **will** 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 **I**nvestigators in this trial and will not otherwise consult for the Sponsor. **SAE information will be provided to the DSMC on an ongoing basis as SAEs occur. Adhoc (closed) DSMC meetings for review of unblinded data from subjects who experience SAEs, as requested by the DSMC, will be arranged.** 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 trial.

Section	Original Text	Revised Text
Section 16.2 Ethical Conduct of the Trial	The trial 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.	The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (**64th WMA General Assembly, Fortaleza, Brazil, October 2013**) and are consistent with ICH/GCP, applicable regulatory requirements.
Section 17.1 AE Reporting	The Investigator is responsible for recording AEs reported by the subject or discovered by any other means during the trial. In agreeing to the provisions of this protocol, the ~~i~~investigator accepts all legal responsibilities for immediate reporting of SAEs to ~~the Medical Monitor~~.	The Investigator is responsible for recording AEs reported by the subject or discovered by any other means during the trial. In agreeing to the provisions of this protocol, the **I**nvestigator accepts all legal responsibilities for immediate reporting of SAEs to the **Sponsor**.
Section 18 Publication Policy	The Sponsor intends to publish the results of all of the clinical trials 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 trial (http://www.icmje.org/ethical_1author.html, accessed May 22, 2013). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators, and others involved, such as statisticians.	The Sponsor intends to publish the results of all of the clinical trials that it sponsors consistent with the Declaration of Helsinki (**64th WMA General Assembly, Fortaleza, Brazil, October 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 trial (http://www.icmje.org/ethical_1author.html, accessed May 22, 2013). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators, and others involved, such as statisticians.

Section	Original Text	Revised Text
Section 19 List of References	~~Vairappan B. Modulation of the DDAH-ADMA pathway with the farnesoid X receptor (FXR) agonist INT-747 restores hepatic enos activity and lowers portal pressure in cirrhotic rats. Hepatology. 2009;50(4 Supplement):336A-7A.~~	**Chapman R. Primary sclerosing cholangitis. Autoimmune Liver Disease. 2011; 39(10):558-591.** **Mookerjee RP, Mehta G, Balasubramaniyan V, et al, Hepatic dimethylarginine-dimethylaminohydrolase1 is reduced in cirrhosis and is a target for therapy in portal hypertension. J Hepatol. 2015 Feb; 62(2):325-331.**
Appendix A List of Planned Laboratory Analytes	Hematology ~~prothrombin time (PT and INR)~~ ~~partial thromboplastin time (PTT)~~	**Coagulation Parameters** **prothrombin time (PT and INR)** **partial thromboplastin time (PTT)**

APPENDIX I. PROTOCOL VERSION 4 – SUMMARY OF CHANGES

Background: Protocol 747-207 has been prepared as a Phase 2 trial to evaluate the potential clinical benefit of obeticholic acid (OCA) in PSC.

Rationale: Version 4 of the protocol includes changes to clarify eligibility criteria.

Summary of Changes: The following revisions were made to the Protocol Version 3 in Protocol Version 4. (Note: Deletions are stricken and additions are indicated in bold font.) Minor grammatical changes are not detailed unless included with other changes (eg, capitalizations, punctuation).

Section	Original Text (Version 3)	Revised Text (Version 4)
Title Page	Original Version: 06 Jun 2014 Version 2: 24 September 2014 Version 3: 26 August 2015	Original Version: 06 Jun 2014 Version 2: 24 September 2014 Version 3: 26 August 2015 **Version 4: 08 February 2016**
Synopsis, ExclusionCriterion #5	Clinical evidence of dominant stricture (~~as evidenced by cholangiography or other appropriate imaging modality within the 12 months prior to Day 0) or current biliary stent~~	Current clinical evidence of dominant stricture**s that are considered clinically relevant in the opinion of the Investigator or current biliary stent at Screening**
Synopsis, ExclusionCriterion #6	Current cholecystitis ~~or gallstones (identified by hepatic imaging)~~	Current cholecystitis **or evidence of current biliary obstruction due to gallstones. Asymptomatic gallstones that are not considered a safety risk in the opinion of the Investigator might be acceptable subject to discussion and agreement with the Medical Monitor**
Synopsis, ExclusionCriterion #10	Known Gilbert's syndrome or elevations in unconjugated (indirect) bilirubin >ULN	Known Gilbert's syndrome **or history** of elevations in unconjugated (indirect) bilirubin >ULN **or unconjugated (indirect) bilirubin >ULN at Screening**
8.3. Subject Exclusion Criteria, ExclusionCriterion #5	Clinical evidence of dominant stricture (~~as evidenced by cholangiography or other appropriate imaging modality within the 12 months prior to Day 0) or current biliary stent~~	Current clinical evidence of dominant stricture**s that are considered clinically relevant in the opinion of the Investigator or current biliary stent at Screening**
8.3. Subject Exclusion Criteria, ExclusionCriterion #6	Current cholecystitis ~~or gallstones (identified by hepatic imaging)~~	Current cholecystitis **or evidence of current biliary obstruction due to gallstones. Asymptomatic gallstones that are not considered a safety risk in the opinion of the Investigator might be acceptable subject to discussion and agreement with the Medical Monitor**

Section	Original Text (Version 3)	Revised Text (Version 4)
8.3. Subject Exclusion Criteria, ExclusionCriterion #10	Known Gilbert's syndrome or elevations in unconjugated (indirect) bilirubin >ULN	Known Gilbert's syndrome **or history** of elevations in unconjugated (indirect) bilirubin >ULN **or unconjugated (indirect) bilirubin >ULN at Screening**
12.2.5 Laboratory Assessments	~~Lp(a)~~	
Appendix A	~~Lp(a)~~	
Appendix A	~~Samples will be assessed for the presence/absence of Lipoprotein X~~	

APPENDIX J. PROTOCOL VERSION 5 – SUMMARY OF CHANGES

Background: Protocol 747-207 has been prepared as a Phase 2 trial to evaluate the potential clinical benefit of obeticholic acid (OCA) in PSC.

Rationale: Version 5 of the protocol includes changes to clarify eligibility inclusion criterion #3 and #9, investigational product storage instructions, clarification for titration adjustments, and clarification for summarizing ECG results. The intention for inclusion criterion #3 is to define the evidence required for diagnosis of PSC, which is, as already stated in inclusion criterion #3, by cholangiography diagnosed at any point in time. The requirement for a mandatory 12-month cholangiogram to diagnose PSC was included in error in the previous version. Inclusion criterion #9 is changed to provide correct examples of barrier methods in the protocol.

Summary of Changes: The following revisions were made to Protocol Version 4 in Protocol Version 5. (Note: Deletions are crossed out and additions are indicated in bold font.) Minor grammatical changes are not detailed unless included with other changes (eg, capitalizations, punctuation).

Section	Original Text (Version 4)	Revised Text (Version 5)
Title Page	~~Original Version: 06 June 2014~~ ~~Version 2: 24 September 2014~~ ~~Version 3: 26 August 2015~~ ~~Version 4: 08 February 2016~~	**Version 5: 18 March 2016**
Synopsis, Methodology	Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg.	Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg. **Intermediate doses (eg, 6.5 mg) may be considered as deemed appropriate by the Investigator. Dose should not exceed 10 mg.**
Synopsis, Inclusion Criterion #3	3. Must have a diagnosis of PSC (based on cholangiography at any point in time)~~ and must have had a cholangiography within the past 12 months~~	Must have a diagnosis of PSC (based on cholangiography at any point in time).
Synopsis, Inclusion Criterion #9	• ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm~~,~~ with spermicide; or	Barrier method, ie, (a) condom (male or female) **with spermicide** or (b) diaphragm with spermicide; or
Synopsis, Investigational Product, Dosage and Mode of Administration	LTSE Phase: All subjects will receive open-label OCA at a starting dose that is dependent upon their dose at completion of DB phase, as well as safety and tolerability. Doses may be 1.5 mg, 3 mg, 5 mg, or 10 mg, ie, 1 or 2 tablets, once daily.	LTSE Phase: All subjects will receive open-label OCA at a starting dose that is dependent upon their dose at completion of DB phase, as well as safety and tolerability. Doses may be 1.5 mg, 3 mg, 5 mg, or 10 mg, ie, 1 or 2 tablets, once daily. **Intermediate doses (eg, 6.5 mg) may be considered as deemed appropriate by the Investigator. Dose should not exceed 10 mg.**
Synopsis, Safety Analyses	Laboratory parameters~~,~~ vital signs~~,~~ ~~and electrocardiograms (ECGs)~~ will be summarized by treatment group using descriptive statistics at Baseline	Laboratory parameters **and** vital signs will be summarized by treatment group using descriptive statistics at Baseline and at each

Section	Original Text (Version 4)	Revised Text (Version 5)
	and at each scheduled post-Baseline visit. The change from Baseline will also be summarized.	scheduled post-Baseline visit. The change from Baseline will also be summarized. **Electrocardiograms (ECGs) will be summarized by treatment group using frequency at each visit. The shift from baseline will also be summarized.**
7.4.2, LTSE Phase	…Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg.	Doses of OCA should be titrated as follows, unless clinically indicated: 1.5 mg to 3 mg, 3 mg to 5 mg, and 5 mg to 10 mg. **Intermediate doses (eg, 6.5 mg) may be considered as deemed appropriate by the Investigator. Dose should not exceed 10 mg.**
8.2 Subject Inclusion Criteria, Inclusion Criterion #3	3. Must have a diagnosis of PSC (based on cholangiography at any point in time) ~~and must have had a cholangiography within the past 12 months~~	Must have a diagnosis of PSC (based on cholangiography at any point in time)**.**
8.2 Subject Inclusion Criteria, Inclusion Criterion #9	• ~~Double~~ barrier method, ie, (a) condom (male or female) or (b) diaphragm~~,~~ with spermicide; or	Barrier method, ie, (a) condom (male or female) **with spermicide** or (b) diaphragm with spermicide; or
10.3 Investigational Product Storage	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~~.	**The** investigational product should be stored in the containers in which it is received from the Sponsor's supplier, **at 15°C to 25°C**.
12.2.4, Electrocardiogram	These ECGs must be clearly labeled with the ~~subject's initials~~, Subject ID number, date and time.	These ECGs must be clearly labeled with the Subject ID number, date and time.
13.5.3, Additional Safety Analyses	Additional safety assessments include vital signs and ECGs. Vital signs ~~and ECGs~~ will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized.	Additional safety assessments include vital signs and ECGs. Vital signs will be summarized by treatment group using descriptive statistics at Baseline and at each scheduled post-Baseline visit. The change from Baseline will also be summarized. **ECGs will be summarized by treatment group using frequency at each**

Section	Original Text (Version 4)	Revised Text (Version 5)
		visit. The shift from baseline will also be summarized.