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

Version 5: 18 March 2016

Sponsor

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
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
CD	Crohn's disease
CRA	Clinical Research Associate
CRF	case report form
DB	double-blind
D/d	day/days
dL	deciliter
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
EOT	end of treatment
ERCP	endoscopic retrograde cholangiopancreatography
FGF	fibroblast growth factor
FU	follow-up
FXR	farnesoid X receptor
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HDL	high density lipoprotein

Abbreviation or Specialist Term	Explanation
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
IBD	inflammatory bowel disease
ID	identification
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
L	liter
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
NAFLD	nonalcoholic fatty liver disease
NMR	nuclear magnetic resonance
OCA	obeticholic acid
PBC	primary biliary cirrhosis
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

Abbreviation or Specialist Term	Explanation
SAR	serious adverse reaction
SUSAR	suspected unexpected serious adverse reaction
Tauro-OCA	tauro-obeticholic acid
TE	transient elastography
TEAE	treatment emergent adverse event
TG	triglycerides
TIPS	transjugular intrahepatic portosystemic shunt
TNF-α	tumor necrosis factor - alpha
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VAS	visual analogue scale
VLDL	very low density lipoprotein
W/wk	week
WBC	white blood cell

3. TRIAL OBJECTIVES AND PURPOSE

3.1. Primary Objective

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

- Serum ALP
- Safety

3.2. 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:
  - FXR activity
  - Inflammatory bowel disease (IBD)
- 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

4. INVESTIGATIONAL PLAN

4.1. 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 4.4.1 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 4.4.2. 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.

4.1.1. Trial Design Diagram

Figure 1: Trial Design Schematic

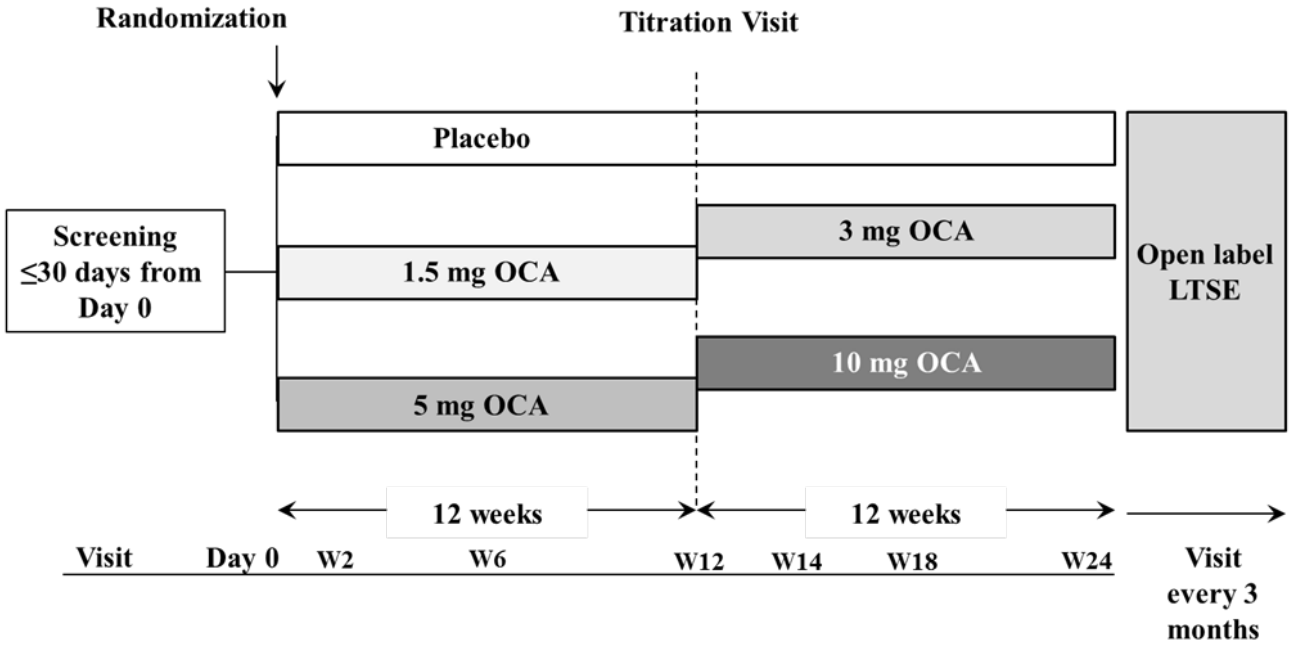

Table 1: Schedule of Trial Procedures: Double-Blind Phase

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	
Hepatic Ultrasound[j]	X							X	
Partial Mayo Score[k,l]	X	X	X	X	X	X	X	X	X
CDAI[l,m]	X	X	X	X	X	X	X	X	X
Pruritus VAS and 5-D[n]		X	X	X	X	X	X	X	X
Adverse Events		X[o]	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[p]			X			X[q]	
Investigational Product Accountability/ Compliance[r]			X	X	X	X	X	X	
Laboratory Evaluations[s]									
Serum Chemistry, Hematology, & Coagulation Parameters	X[t]	X	X	X	X	X	X	X	X
FGF-19		X			X			X	
Plasma Bile Acids		X			X			X	
C4		X			X			X	
Apolipoprotein & NMR Lipoprotein Panel		X			X			X	
Dipstick Urinalysis	X	X			X			X	
Urine Pregnancy Test[u]	X	X			X			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 6.1).
[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] 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. Diary card data from the Screening period are collected at the Day 0 visit.
[m] CDAI completed only for subjects with CD.
[n] Questionnaire completed by the subject.
[o] Adverse events will be collected from the time that signed informed consent is obtained.
[p] 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 6.1).
[q] 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.)
[r] Investigational product accountability/compliance will include review of tablets and bottles dispensed and returned at each clinic visit
[s] All laboratory samples (except urine and serum pregnancy test, if applicable) are analyzed by the Central Laboratory.
[t] IgG4 is included in the assessment panel at Screening only.
[u] 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 5.1 for procedures to be followed for a subject whose pregnancy is early terminated and wishes to continue in the trial.

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	
Hepatic Ultrasound[i]	X					X				X	
Partial Mayo Score[j,k]	X		X	X	X	X	X	X	X	X	X
CDAI[k,l]	X		X	X	X	X	X	X	X	X	X
Pruritus VAS and 5-D[m]	X		X	X	X	X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X	X	X	X
Dispense Investigational Product	X[n]		X	X	X	X	X	X	X		
Investigational Product Accountability/ Compliance[o]	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[p]											
Serum Chemistry, Hematology, & Coagulation Parameters	X		X	X	X	X	X	X	X	X	X
FGF-19	X					X				X	
Plasma Bile Acids & C4	X			X		X				X	
Apolipoprotein & NMR Lipoprotein Panel	X										
Dipstick Urinalysis	X			X		X		X		X	
Urine Pregnancy Test[q]	X		X	X	X	X	X	X	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 6.1).
[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] 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).
[j] Partial Mayo score completed only for subjects with UC.

[k] 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.
[l] CDAI completed only for subjects with CD.
[m] Questionnaire completed by the subject.
[n] 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.)
[o] Investigational product accountability / compliance will include review of tablets and bottles dispensed and returned at each clinic visit.
[p] All laboratory samples (except urine and serum pregnancy test, if applicable) are analyzed by the Central Laboratory.
[q] 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 5.4.1 for procedures to be followed for a subject whose pregnancy is early terminated and wishes to continue in the trial.

4.1.2. 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.

4.2. Number of Subjects

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

4.3. 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 6.4.1) and then randomized in equal proportions to each of the treatment groups.

4.4. Dose Adjustment Criteria and Dose Titration

4.4.1. 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.

4.4.2. 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.

4.4.3. 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 4.5 details the criteria for trial termination. Reasons for discontinuation of individual subjects are noted in Section 5.4.1 and Section 5.4.2.

4.5. 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.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. 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).

5.2. Subject Inclusion Criteria

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

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

5. 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.
6. 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.

7. 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.
8. 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)]

5.3. 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.

5.4. Subject Withdrawal Criteria

5.4.1. 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 8.1.9).

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

5.4.2. 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 5.3) 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 8.1.3.1 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 8.1.3.1, should be discontinued from the trial.

5.4.3. 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.

6. TREATMENT OF SUBJECTS

6.1. 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 4.4.2 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	-

6.2. 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.

6.2.1. 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.

6.2.2. 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).

6.2.3. 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 5.4.2).

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

6.3. 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.

6.4. 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 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.

6.4.1. 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

7. ASSESSMENTS OF EFFICACY

7.1. 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 4.1).

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.

7.2. Primary Efficacy Assessments

The primary efficacy assessment is serum ALP.

7.3. 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)

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 A.

- 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 C.

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 B.

- 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).

8. 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.

8.1. Adverse Events and Serious Adverse Events

8.1.1. Definitions

8.1.1.1. 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.

8.1.1.2. 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.

8.1.1.3. 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.

8.1.2. 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.

8.1.3. 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.

8.1.3.1. 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.

8.1.4. Reporting of Adverse Events and Serious Adverse Events

8.1.4.1. 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.

8.1.4.2. 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.

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.

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.

8.1.5. 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

8.1.6. 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.

8.1.7. 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 8.1.4.2.

8.1.8. 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.

8.1.9. 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.

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.

8.2. Other Safety Parameters

8.2.1. 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.

8.2.2. 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.

8.2.3. 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.

8.2.4. 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.

8.2.5. 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 8.1.9 until pregnancy outcome.

9. STATISTICS

9.1. 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.

9.2. 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.

9.3. 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.

9.3.1. 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.

9.3.2. 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.

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

9.4. Safety Analysis

9.4.1. 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.

9.4.2. Clinical Laboratory Evaluations

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).

9.4.3. 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.

9.5. Interim Analyses and Data Monitoring

9.5.1. 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.

9.5.2. 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.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. 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.

10.2. 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.

11. 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.

12. ETHICS

12.1. 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. 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.

12.2. 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.

13. LIST OF REFERENCES

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

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.

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

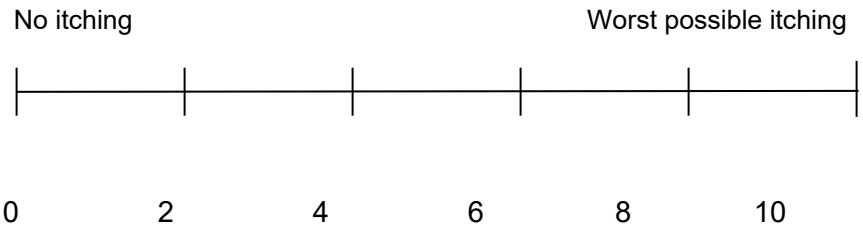
Partial Mayo Scoring System for Assessment of Ulcerative Colitis Activity (The Partial Mayo Score ranges from 0-9, with higher scores indicating more severe disease)
Stool Frequency (Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency) 0 = Normal 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

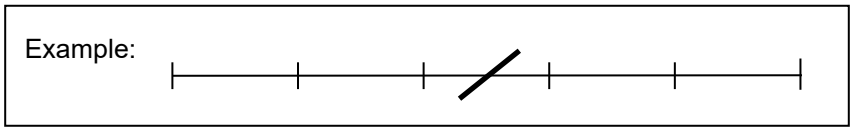
APPENDIX B. PRURITUS VISUAL ANALOGUE SCALE

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 C. 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 D. PROTOCOL VERSION 3: 26 AUGUST 2015 – 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.

Section	Original Text	Revised Text
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.	*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.
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*	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**

Section	Original Text	Revised 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.	**procedures have been completed (except dispensing of open-label investigational product).** **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).**
	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**. Diary card data from the Screening period are collected at the Day 0 visit.**
	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 q: 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	Original Text	Revised Text
	Footnote r: Investigational product is dispensed only for subjects who continue into the LTSE.	
Schedule of Trial Procedures, Table 2 LTSE Phase	*No Text* Serum Chemistry & Hematology Footnote c: The LTSE D1 is also the final visit (Week 24) of the DB treatment period. *No Text*	**Contact Wk2 ±3d – Safety Contact** Serum Chemistry, Hematology**, & Coagulation Parameters** 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).** Footnote g: **The Safety Contact can be either via telephone or email, and does not require an onsite visit.** Footnote i: **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 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**.**

Section	Original Text	Revised Text
		Footnote **m**: Questionnaire completed **by** the subject. Footnote n: **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.)**
	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*	
Section 7.4.2 LTSE Phase	~~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:~~ 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. ~~Subjects may be titrated in the order~~ 1.5 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.** The guideline for an increase in the dose of open-label OCA is based on the goal of achieving ALP <1.5x ULN and

Section	Original Text	Revised Text
	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.~~	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.~~	**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.**
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 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.	**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 **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.**

Section	Original Text	Revised Text
	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 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~~nvestigator to be clinically important	**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**.** Ther**e 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. 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	Original Text	Revised Text
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 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	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.	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~~)	Relevant information about all concomitant drugs (including prescribed, over-the-counter, or herbal preparations) taken prior to (ie, within 30 days of

Section	Original Text	Revised Text
	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.	**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 9.6.1 Visit Windows	The Screening visit should occur ≤30 days prior to the Day 0 visit. 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 Follow-Up visit, which should occur within ± 1 week.	The Screening visit should occur ≤30 days **(ie, Day -30 to Day -1)** prior to the Day 0 visit. 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**

Section	Original Text	Revised Text
		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: Record prior (within 30 days of ~~Day 0~~) and current concomitant medications 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	Screening **v**isit procedures are as follows: Record prior (within 30 days of **Screening**) and current concomitant medications**.** **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.**

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)**.
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	Obtain blood samples for: Serum chemistry**,** hematology**, and coagulation** FGF-19
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 10.4 Investigational Product Administration	Subjects must be instructed to swallow the indicated number of tablets whole; they must not chew, divide, or crush the tablets.	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	Original Text	Revised Text
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 12.1.3.1 Severity of Pruritus	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.	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 12.1.8 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	~~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.	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.**
Section 13.6.1 Interim Analysis	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.	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 13.6.2 Data and Safety Monitoring Committee	An independent DSMC will review safety data ~~at periodic intervals~~ from this 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**. **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.**

APPENDIX E. PROTOCOL VERSION 4: 08 FEBRUARY 2016 – 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.

Section	Original Text (Version 3)	Revised Text (Version 4)
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**
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 F. PROTOCOL VERSION 5: 18 MARCH 2016– 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.

Section	Original Text (Version 4)	Revised Text (Version 5)
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	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
13.5.3, Additional Safety Analyses		**ECGs will be summarized by treatment group using frequency at each visit. The shift from baseline will also be summarized.**