



Clinical Study Protocol 747-214

OBETICHOLIC ACID (OCA) AND BEZAFIBRATE (BZF)

**A Phase 2a, Double-Blind, Randomized, Active Controlled, Parallel Group
Study Evaluating the Efficacy, Safety, and Tolerability of Bezafibrate
Administered in Combination with Obeticholic Acid in Subjects with Primary
Biliary Cholangitis**

Version 6: 20 December 2023

EudraCT number: 2022-001241-20

ClinicalTrials.gov Identifier: NCT05239468

Sponsor

**Intercept Pharmaceuticals, Inc.
305 Madison Avenue
Morristown, NJ 07960
USA**

TEL: +1 858 652 6800

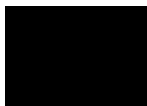
FAX: +1 858 558 5961

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:



Electronically signed by: 

Reason: I have reviewed this document

Date: Dec 20, 2023 10:43 EST

20-Dec-2023



MD
Clinical Development
Intercept Pharmaceuticals, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochures (IB) for obeticholic acid (OCA) and the fixed-dose combination (FDC) (OCA and bezafibrate [BZF]), and this Protocol 747-214. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA and BZF to selected subjects according to this protocol.

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

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

By my signature below, I hereby attest that I have read, understood, and agreed to abide by all the conditions, instructions, and restrictions contained in Protocol 747-214 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

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

Investigator's Name (Printed)

Investigator's Signature

Date

STUDY PERSONNEL CONTACT INFORMATION

Medical Monitor

Primary Contact:

[REDACTED] MD

[REDACTED]

Fortrea

Phone: [REDACTED]

Email: [REDACTED]

Secondary Contact:

[REDACTED], MD, PMBA

[REDACTED], Clinical Development

Intercept Pharmaceuticals, Inc. (Intercept)

Morristown, NJ 07960

Mobile: [REDACTED]

Email: [REDACTED]

Telephone (24 hours):

+1 844 662 3512

SAE Contact Information

SAE Fax:

+1 800 497 8521

SAE Email:

sac@interceptpharma.com

2. SYNOPSIS

Name of Sponsor/Company: Intercept Pharmaceuticals, Inc.	
Name of Investigational Products: Obeticholic acid (OCA), bezafibrate (BZF), and matching placebo	
Name of Active Ingredient: Obeticholic acid; 6 α -ethyl-chenodeoxycholic acid; INT-747 Bezafibrate	
Title of Study: A Phase 2a, Double-Blind, Randomized, Active Controlled, Parallel Group Study Evaluating the Efficacy, Safety, and Tolerability of Bezafibrate Administered in Combination with Obeticholic Acid in Subjects with Primary Biliary Cholangitis	
Investigators and/or Study Center(s): Approximately 64 investigational sites, globally	
Studied Period: Estimated date first subject enrolled: Aug 2021 Estimated date last subject completed: Aug 2025	Phase of Development: Phase 2a
Objectives: <u>Primary Objective:</u> The primary objective is to assess the effects of the combination of OCA and BZF on alkaline phosphatase (ALP) in comparison to BZF alone in subjects with primary biliary cholangitis (PBC)	
<u>Secondary Objectives:</u> To assess the effects of the combination of OCA plus BZF versus BZF alone in subjects with PBC on the following: - Biochemical disease markers, including ALP, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and conjugated bilirubin, and lipid panel - Biomarkers of bile acid synthesis and homeostasis, including 7α-hydroxy-4 cholesten-3-one (C4) and bile acids - Safety and tolerability	
<u>Additional Objectives:</u> 	

Methodology:

Overview: This Phase 2a, randomized, DB, active-controlled, parallel-group study will evaluate the efficacy, safety, and tolerability of OCA (5 mg/day) administered in combination with 2 different BZF doses (100 and 400 mg/day) compared to BZF alone (at 2 doses, 100 and 400 mg/day) in up to 60 subjects with PBC over at least 12 weeks.

Screening Phase (2 and up to 8 Weeks): Subjects will be screened for up to 8 weeks before being randomized into the study to allow for the collection of repeat serum chemistry samples (there will be 2 screening visits at least 2 weeks apart) for verification of inclusion/exclusion criteria and to establish baseline (including Day 1).

Double-blind Phase (12 Weeks): Subjects who meet the entry requirements will be randomized in a 1:1:1:1 ratio on Day 1 to receive either Treatment A (BZF 100 mg immediate-release [IR] once daily), Treatment B (BZF 400 mg IR once daily), Treatment C (OCA 5 mg once daily + BZF 100 mg IR once daily), or Treatment D (OCA 5 mg once daily + BZF 400 mg IR once daily). The DB Phase will extend from Day 1 through Week 12; eligible subjects will then continue into the LTSE Phase through the end of the study.

Once a subject is scheduled to be enrolled the clinical site will inform the unblinded statistician via secured and restricted email (unblindedstats@interceptpharma.com) at least 3 to 4 days prior to dosing. The unblinded statistician will allocate the first 3 subjects in each treatment arm to PM dosing and will send an email to the site to provide dosing time (i.e., AM or PM). The Interactive Response Technology (IRT) system will notify the unblinded statistician by an auto-generated alert after the first 3 subjects in one treatment arm are randomized. All subsequent subjects in the same treatment arm will be allocated to AM dosing. The unblinded statistician responsible for randomization will not be involved in the regular study operations and will have no communication with study team members or be involved in the interim analyses. Investigational products will be taken orally once daily for the duration of the study. Subjects assigned to AM dosing will be instructed to begin dosing on Day 1 and to take investigational product between 7 AM-11 AM each day. Subjects assigned to PM dosing will take investigational product between 2 PM-5 PM for the entire DB Phase. After the completion of the DB Phase, all subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits).

Subjects must be instructed to swallow the tablets whole; investigational product must not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout study conduct.

After the Day 1 Visit, subsequent study visits during the DB Phase will occur at approximately Weeks 2, 4, 6, 8, 10 and 12 (Day 1 of LTSE) for the assessment of efficacy, safety, tolerability, and PK. These visits will also allow for the assessment of any AEs, changes to concomitant medications and/or new medications that have been initiated, medical/surgical procedures, and to verify that the subject is dosing as directed. A rolling evaluation of available efficacy and safety data may occur periodically during the DB Phase.

To preserve the study blind, appearance-matched placebo tablets for OCA and/or BZF will be administered to subjects in each treatment group as shown in the study design diagrams during the DB treatment phase.

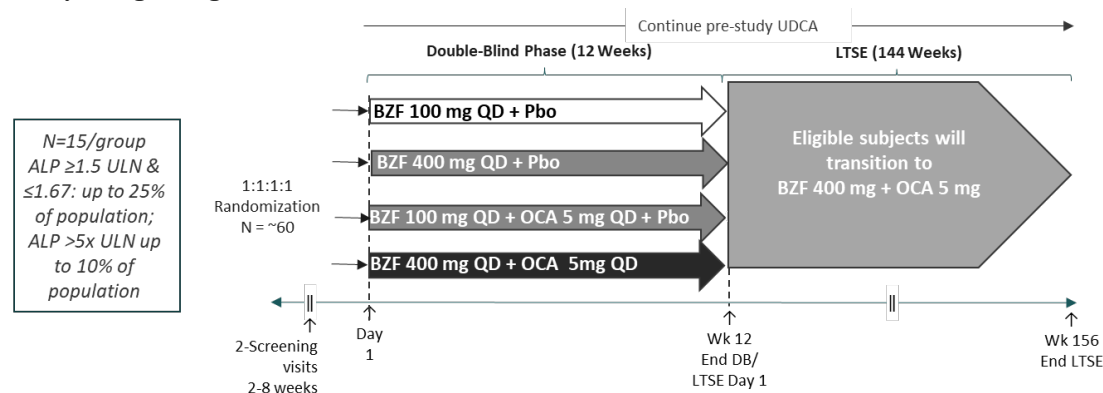
Randomization will be stratified by:

- Total bilirubin level ($\leq 0.7x$ or $>0.7x$ upper limit of normal [ULN] but $<2x$ ULN)
- ALP $\geq 1.5x$ ULN but $\leq 1.67x$ ULN (not more than 25% of subjects enrolled)
- ALP $>1.67x$ ULN (remaining subjects enrolled)

Note: The total subject population will also include up to 10% of subjects with baseline ALP $>5x$ ULN.

LTSE Phase (144 weeks): Subjects who continue to meet protocol requirements will transition directly to the LTSE Phase (an open-label design) upon completion of the Week 12 visit of the DB Phase. The end of the 12-week DB Phase becomes Day 1 of the LTSE Phase. All subjects transitioning into the LTSE Phase will receive treatment with OCA 5 mg once daily + BZF 400 mg IR once daily (Treatment D of the DB Phase). Subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits).

Study Design Diagram of the Double-Blind and LTSE Phases



ALP = alkaline phosphatase; BZF = bezafibrate; DB = double blind; LTSE = long-term safety extension; OCA = obeticholic acid; Pbo = placebo; QD = once daily; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; Wk = week

Note: First 3 subjects per treatment group will be assigned to PM dosing.

Note: Placebo = either OCA or BZF tablets.

Note: Subjects taking UDCA at the time of enrollment will remain on their stable dose of UDCA during the study.

Note: LTSE Day 1 will be the last visit in the DB Phase (Week 12).

Note: Subjects who transition to the LTSE Phase will receive OCA 5 mg + BZF 400 mg IR QD.

Number of Subjects (Planned):

Approximately 60 subjects (15 per group) will be enrolled and randomized in a 1:1:1:1 ratio to 1 of 4 treatment arms (Treatments A, B, C, or D).

Diagnosis and Main Criteria for Inclusion:

1. A definite or probable diagnosis of PBC (consistent with the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines [Lindor 2009a; EASL 2017]), as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:
 - History of elevated ALP levels for at least 6 months
 - Positive antimitochondrial antibody (AMA) titer, or if AMA negative or low titer ($\leq 1:80$), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (pyruvate dehydrogenase-E2, 2-oxo-glutaric acid dehydrogenase complex)
 - Liver biopsy results consistent with PBC (collected at any time before Screening)
2. At least one of the following qualifying biochemistry values (the mean of both Screening visits):

- ALP $\geq 1.5 \times$ ULN but $\leq 1.67 \times$ ULN (will not exceed 25% of subjects enrolled in the study)
 - ALP $> 1.67 \times$ upper limit of normal (ULN) (including up to 10% of subjects with ALP $> 5 \times$ ULN)
 - Total bilirubin $> \text{ULN}$ but $< 2 \times \text{ULN}$
3. Age ≥ 18 years
 4. Taking UDCA for at least 12 months (stable dose for ≥ 3 months) before Day 1 or no UDCA for 3 months before Day 1
 5. Contraception: Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥ 1 highly effective method of contraception during the study and for 30 days after the end of treatment. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from exposure to investigational medicinal products.
 - Intrauterine device
 - intrauterine device (IUD)
 - intrauterine hormone-releasing system (IUS)
 - Bilateral tubal occlusion
 - Vasectomy (partner)
 - Combined (estrogen and progestogen containing) hormonal contraception (e.g., oral, intravaginal or transdermal) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
 - Progestogen-only hormonal contraception (e.g., oral, injectable or implantable) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
 - Sexual abstinence, as a form of highly effective contraception, is defined as avoiding all types of sexual activity that could result in pregnancy during the entire period of the study treatment until at least 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study, including the LTSE Phase.
 6. Must provide written informed consent and agree to comply with the study protocol

Key Exclusion Criteria:

1. History or presence of other concomitant liver diseases including any of the following:
 - Hepatitis C virus (HCV) infection and ribonucleic acid positive
 - Active Hepatitis B virus (HBV) infection; however, subjects who have seroconverted [hepatitis B surface antigen negative (sAg-), hepatitis B surface antibody positive (sAB+); hepatitis B e-antigen negative (eAg-), hepatitis B e-antibody positive (eAb+); HBV DNA negative] may be included in this study after consultation with the Medical Monitor
 - Subjects should be excluded if positive HBV DNA or HCV RNA
 - Primary sclerosing cholangitis
 - Alcoholic liver disease
 - Definite autoimmune liver disease or PBC-AIH overlap
 - Non-Alcoholic Steatohepatitis (NASH)
 - Gilbert's Syndrome (due to interpretability of bilirubin levels)
 - Rare liver conditions such as Wilson's disease, hemochromatosis, alpha-one anti-trypsin deficiency, or other conditions identified by the Investigator

2. Clinical complications of PBC including:
 - History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
3. History or presence of any of the following decompensating events:
 - CP-Score ≥ 7
 - Clinical evidence of decompensated liver disease or portal hypertension
 - Varices (including a history of esophageal varix ligation)
 - Ascites/hepatic hydrothorax
 - Spontaneous bacterial peritonitis
 - Hepatic encephalopathy
 - Jaundice (with total bilirubin >3 mg/dL [$>51.3 \mu\text{mol/L}$])
 - Biochemical evidence of hepatic impairment, hepatic decompensation, or injury including at least one of the following:
 - Total bilirubin >3 mg/dL ($>51.3 \mu\text{mol/L}$)
 - INR >1.7
 - Albumin <3.5 g/dL
 - MELD >12
 - ALT >5X ULN
 - Known or suspected hepatocellular carcinoma (HCC)
 - Prior trans-jugular intrahepatic portosystemic or peritoneovenous shunt procedure
 - Hepatorenal syndrome (type I or II) or serum creatinine >1.5 mg/dL ($135 \mu\text{mol/L}$) at Screening Visits 1 and 2
 - Portopulmonary hypertension
 - Hepatopulmonary syndrome
4. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) or which may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions)
5. Presence of any other disease or condition that interferes with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine (e.g., inflammatory bowel disease or gastric bypass procedure [gastric lap band is acceptable])
6. History of or current gallbladder diseases:
 - Cholelithiasis or cholecystitis without prior cholecystectomy
 - Choledocholithiasis without documented complete stone removal (e.g., via ERCP) and cholecystectomy
 - Any size symptomatic gallbladder polyp
 - Gallbladder polyp >5 mm
7. History or current pancreatitis
8. History of drug-induced myopathy
9. Chronic kidney disease (CKD) (serum creatinine >1.5 mg/dL [$>135 \mu\text{mol/L}$]; creatinine clearance $\leq 60 \text{ mL/min}$) or undergoing dialysis

10. Platelet count <150,000/ μ L at Screening Visits 1 and 2 (an average of both Screening visits)
11. Known history of human immunodeficiency virus (HIV) infection
12. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or Screening (pretreatment) QT or QTc interval of >450 milliseconds for males and >470 milliseconds for females
13. Severe pruritus, as defined in [Table 15](#), or required systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin) within 2 months of Day 1. Subjects who plan to use or will use BAS during the study will not be eligible.
14. History of known or suspected clinically significant (CS) hypersensitivity to OCA, BZF, or other fibrates or any of their components
15. Known photoallergic or phototoxic reactions to fibrates
16. If female, known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
17. Other CS medical conditions that are not well controlled or for which medication needs are anticipated to change during the study (e.g., Type 2 diabetes mellitus, hypothyroidism, nephritic syndrome, dysproteinemia, obstructive biliary disease, dyslipidemia), and/or up to the discretion of the Principal Investigator
18. Treatment with the following medications 30 days before Day 1 or plans to use these medications during the study: azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, statins, budesonide and other systemic corticosteroids, monoamine oxidase inhibitors (MAOIs), and potentially hepatotoxic drugs (including α -methyl-dopa, sodium valproic acid, isoniazide, and nitrofurantoin)
19. Treatment with the following medications 12 months before Day 1 or plans to use these medications during the study: antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
20. Participation in a study of another investigational medicine or device within 30 days before Screening
21. Treatment with commercially available OCA or participation in a previous study involving OCA or other FXR agonists, or peroxisome proliferator activated receptor (PPAR)-agonists within 3 months before Screening
22. Unable to tolerate BZF or other fibrates, treatment with commercially available fibrates, or participation in a previous study involving fibrates within 3 months before Screening
23. History of or ongoing alcohol or drug abuse within 1 year before Day 1. Subjects with moderate alcohol use within the past 3 months will be excluded from this study. Moderate alcohol consumption is defined as 1 standard drink per day for women and 2 drinks per day for men; whereby 1 standard drink is equivalent to: 12 oz beer (5% alcohol); 5 ounces of wine (12% alcohol), and 1.5 ounces of 80 proof (40% alcohol)
24. History of noncompliance with medical regimens, or is considered by the investigator not able to meet the requirements as specified in the protocol at the Screening visits and throughout the duration of the study
25. Blood or plasma donation within 30 days before Day 1
26. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
27. A CK value at Screening $\geq 5 \times$ ULN or any abnormal laboratory value that is considered CS in the opinion of the Investigator and Sponsor (at either Screening visit)

28. Known or suspected nephrotic syndrome based on the following diagnostic criteria (both Type 1 and Type 2):

- Proteinuria, spot urine protein: albumin/creatinine ratio (ACR) of >300 mg/mmol (subjects with normal renal function and ACR values analyzed to be below the lower limits of detection are permitted)
- Serum albumin <25 g/L
- Clinical evidence of peripheral edema
- Severe hyperlipidemia (total cholesterol above >10 mmol/L)

For US sites where HepQuant SHUNT will be conducted, the following exclusion criteria will only apply for subjects who are participating in the HepQuant SHUNT procedure:

29. Subjects with a history of known or suspected hypersensitivity to any ingredient in human albumin preparations
30. Subjects with uncontrolled hypertension (defined as a diastolic blood pressure of 110 mmHg or higher)
31. Subjects with extensive resection of large segments of small intestine (short gut) or severe gastroparesis
32. Subjects on either a non-selective beta blocker or an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) who are unwilling to delay taking their normal dose the morning of their testing

Hepatic Safety Adjudication:

All potential events of hepatic injury will be adjudicated in all enrolled subjects that occur after administration of the first dose of investigational product during the double-blind and LTSE phase. Potential events of hepatic injury will be reviewed by the blinded Hepatic Safety Adjudication Committee (HSAC).

Specific details of the events that will be adjudicated are described in the respective adjudication charter. Any changes to either the adjudication process or changes to specific events to be adjudicated will be addressed in the charters and will be communicated to all study sites outside of a protocol amendment.

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

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

Investigational Products, Dosage, and Mode of Administration:

All tablets must be swallowed whole and not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout the study period. Subjects are requested to take medication at their assigned dosing time (AM or PM). Specific instructions for dosing will be provided for PK assessment days.

Double-Blind Phase:

- OCA placebo tablet, once daily

- OCA 5 mg tablet, once daily
- BZF placebo tablet, once daily
- BZF 100 mg IR tablet, once daily
- BZF 200 mg IR tablet, once daily (2 x BZF 200 mg IR tablets for BZF 400 mg IR once daily)

The OCA and BZF investigational product will be dispensed for oral administration in dosing kits that contain 1 bottle of OCA or placebo and weekly blister wallets that contain the active BZF dose (100 mg IR or 400 mg IR) or placebo. Each subject should take 3 tablets daily, one tablet from the OCA bottle and 2 tablets from the weekly blister wallet.

LTSE Phase:

- OCA 5 mg tablet, once daily
- BZF 200 mg IR tablet, once daily (2 x BZF 200 mg IR tablets for BZF 400 mg IR once daily)

The OCA and BZF investigational products will be dispensed for oral administration in dosing kits that contain 1 bottle of OCA 5 mg tablets and weekly blister wallets that contain the active BZF 400 mg IR dose. Each subject should take 3 tablets daily, one tablet from the OCA bottle and 2 tablets from the weekly blister wallet.

Duration of Treatment:

The total duration of the study per subject will be a DB duration of 12 weeks and LTSE up to 144 weeks. Subjects who continue to meet protocol requirements will transition directly into the LTSE Phase once they complete the 12-week DB Phase.

Statistical Methods:

Analysis Populations:

ITT Population: The Intent-to-Treat (ITT) Population will include all randomized subjects. Treatment assignment will be based on the randomized treatment.

mITT Population: The modified ITT (mITT) Population will include all randomized subjects who have baseline and at least one post-baseline ALP assessment. Treatment assignment will be based on the randomized treatment.

Safety Population: The Safety Population will include all randomized subjects who receive at least 1 dose of BZF and/or OCA. Treatment assignment will be based on the actual treatment received.

Pharmacokinetic Population: The PK Population will include all subjects who receive OCA and/or BZF and have enough quantifiable PK samples without any major protocol deviations that could potentially affect plasma exposure.

LTSE Population: The LTSE Population will include all subjects who receive at least 1 dose of investigational product, during the LTSE phase.

Primary Efficacy Analyses in Double-Blind Phase:

Analysis on Primary Efficacy Endpoint: The primary efficacy endpoint is the change in ALP from baseline to Week 12 in the DB Phase.

The Primary Efficacy Analysis for the DB Phase will be conducted using the mITT Population when all subjects have completed the DB Phase.

Analyses of change in ALP will be carried out using a mixed-effect repeated measures model (MMRM) to evaluate the effect of treatment groups over time based on the mITT Population. The dependent variable will be the change in ALP from baseline. The model will include the terms of treatment group, visit, treatment by visit interaction, randomization stratification variables as factors and baseline value as covariate.

Analyses of Secondary and Additional Efficacy Endpoints: The ITT Population will be the primary population used for the secondary and additional efficacy analyses.

The secondary efficacy endpoints include:

- The response rates of $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ reduction from baseline at Week 12, and normalization rates of ALP at Week 12
- Normalization rates at Week 12 of GGT, ALT, AST, ALP, total and conjugated bilirubin, and lipid panel
- Change from baseline to Week 12 in GGT, ALT, AST, and total and conjugated bilirubin, and lipid panel
- Change from baseline to Week 12 in 7α -hydroxy-4-cholesten-3-one (C4) and bile acids

All continuous and categorical secondary and additional efficacy endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit comparing the BZF and OCA + BZF treatment groups.

Analyses for ALP response rates of $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ reduction from baseline at Week 12, and normalization rates and percentage of subjects with ALP $< 1.67 \times$ ULN and total bilirubin $\leq$ ULN and ALP decrease of $\geq 15\%$ from baseline will be performed using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

For the rolling interim analysis (described below in the Interim Analyses Section), if data are insufficient for the MMRM model or the Cochran-Mantel-Haenszel test, a simpler model or test may be used.

[REDACTED] will be performed using a MMRM model similar to that for the primary efficacy analysis.

Additional details regarding the planned analyses, methods, and outputs for the study will be included in the statistical analysis plan (SAP).

Safety Analyses in Double-Blind Phase

The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment received.

Safety data, including serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), physical examinations, electrocardiograms (ECGs), vital signs, clinical laboratory assessments, and treatment discontinuations, will be compared across all treatment groups during the DB Phase.

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

Laboratory parameters and vital signs will be summarized (including Hy's law) by treatment group using descriptive statistics at baseline and at each scheduled postbaseline 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 before treatment.

Interim Analyses

The Sponsor will use data output from interim analyses from the DB phase for purposes of regulatory interactions and subsequent Phase 3 trial design planning. The SAP will specify the methods for the interim analyses, as well as additional details on the conduct.

Rolling Interim Analysis

The Sponsor will perform an unblinded rolling analysis of efficacy, PK, and safety data throughout the DB phase. Details of the unblinding and Data Access Plan, including Sponsor Staff that will be unblinded, will be provided in separate documents. All PIs and site staff and patients will remain blinded throughout the study.

The efficacy measures for the rolling interim analysis include:

- Primary Endpoint: The change in ALP from baseline to Week 12 in the DB Phase in the mITT Population
- Secondary Endpoints:
 - The ALP response rates of $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ reduction from baseline at Week 12 and the normalization rates of ALP at Week 12 in ITT Population
 - The changes from baseline to Week 12 in GGT, ALT, AST, total bilirubin, and conjugated bilirubin, and lipid panel in ITT Population
- Additional Endpoint:
 - [REDACTED]

In addition, analyses of drug exposure and safety assessments will be performed.

DMC Interim Safety Analysis

The Data Monitoring Committee (DMC) will perform an interim safety analysis when approximately 32 subjects complete the Week 12 visit in accordance with the DMC Charter. The DMC will review the interim criterion for safety data and other relevant information to determine whether to recommend and continue the study.

LTSE Analyses

Similar analyses to those described for the DB Phase (including drug exposure) will be conducted for the LTSE Phase, using the DB baseline value. Analyses based on the DB baseline will be performed using randomized treatment groups in the DB Phase.

HepQuant-SHUNT in LTSE Phase

Liver function as assessed by the HepQuant-SHUNT test will be summarized by treatment group using descriptive statistics at Week 60. Details on the analysis of Disease Severity Index, a marker of liver function, will be specified in the SAP.

Sample Size Determination

Assuming the change from baseline of ALP in BZF is -146 U/L, 15 subjects per arm will provide 80% power to detect a treatment difference of 60 U/L between a BZF arm and BZF+OCA arm at two-sided alpha of 0.05 with the pooled standard deviation of 58.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
████	████████████████
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	biliary atresia
BAS	bile acid sequestrants
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
BZF	Bezafibrate
████	████████████
C4	7α-hydroxy-4-cholesten-3-one
████	████████████
CCDS	Company Core Data Sheet
CDCA	chenodeoxycholic acid
CI	confidence interval
CK	creatinine kinase
C _{max}	peak (maximum) plasma concentration
CP	Child-Pugh
CRA	Clinical Research Associate
CS	clinically significant
DB	double-blind
DILI	drug-induced liver injury
DMC	data monitoring committee
DSI	Disease Severity Index
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form

Abbreviation or Specialist Term	Explanation
eGFR	estimated glomerular filtration rate
█	█
EMA	European Medicines Agency
EOS	end of study
█	█
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FDC	fixed dose combination
█	█
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLOBE score	a risk score used to predict transplantation-free survival
HbsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCP	healthcare provider
HCV	hepatitis C virus
HDLc	high-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HSAC	Hepatic Safety Adjudication Committee
hs-CRP	high-sensitivity c-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IR	immediate release
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intent-to-Treat
IWRS	interactive web response system
LTSE	long-term safety extension
MAOI	monoamine oxidase inhibitor

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect repeated measures model
MRS	Mayo Risk Score
NASH	nonalcoholic steatohepatitis
OCA	obeticholic acid
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PMR	post-marketing requirement
PPAR	peroxisome proliferator-activated receptor
PSC	primary sclerosing cholangitis
PT	prothrombin time
QD	once daily
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SmPC	Summary of Product Characteristics
SR	sustained release
SUSAR	suspected unexpected serious adverse reaction
T3	Triiodothyronine
T4	Thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
TT	triple therapy
UDCA	Ursodeoxycholic acid
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale

5. INTRODUCTION

5.1. Overview of Primary Biliary Cholangitis, Obeticholic Acid, and Bezafibrate

Primary biliary cholangitis (PBC) is a rare, autoimmune, cholestatic liver disease, predominantly affecting women over 40 years of age ([EASL 2017](#), [Lindor 2019](#)). It is estimated that the prevalence of PBC is 1 in 1000 women over the age of 40 years with up to 100,000 patients diagnosed with PBC in the United States (US); less than 10% of patients with PBC are male ([EASL 2017](#)). The natural history of the disease is well understood and characterized by progressive destruction of intrahepatic bile ducts resulting in chronic cholestasis, portal inflammation, and fibrosis that can lead to cirrhosis and ultimately liver failure ([Murillo Perez 2020](#); [Selmi 2011](#)).

The most common presenting symptoms of PBC are pruritus and fatigue. The diagnosis of PBC can be met with at least 2 of the following criteria: 1) biochemical evidence of cholestasis with elevation of serum ALP; 2) presence of anti-mitochondrial autoantibodies (AMA), or other PBC-specific autoantibodies; or 3) histological evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts ([Lindor 2019](#)).

The treatment goal for patients with PBC is to improve transplant-free survival. Historically, ALP and bilirubin levels have been the primary biochemical markers used by clinicians to determine the risk of progression and to evaluate response to treatment ([Kowdley 2022](#), [Murillo Perez 2020](#), [Corpechot 2011](#), [Lammers 2014](#)). Recent data suggest that optimal survival benefit is realized when normalization of either ALP ($<ULN$) or total bilirubin ($<0.6 \times ULN$) are achieved ([Murillo Perez 2020](#)). High GGT levels have also been associated with increased risk of mortality and liver transplant, supporting the role of GGT as an additional prognostic biomarker of PBC ([Gerussi 2021](#)). AST and ALT may also provide additional prognostic information as the AST/ALT ratio is associated with disease progression, particularly in patients with advanced histologic stages III to IV ([Gatselis 2020](#), [Trivedi 2014](#)). The relative importance of each of these plasma biomarkers remains a key focus of clinical research. It is also increasingly clear that the amount of time an individual spends with abnormal biochemistries is predictive of increased risk ([Kowdley 2023](#), [Soret 2021](#)).

Ursodeoxycholic acid (UDCA), the only approved first-line treatment for PBC, has been demonstrated to provide an insufficient response in many patients. The addition of obeticholic acid (OCA) as a second agent has been shown to improve biochemical responses in ALP and bilirubin for up to 6 years through long-term, open-label extensions of clinical studies. However, despite substantial reductions in ALP and bilirubin, many patients with PBC administered UDCA and OCA remain at an elevated risk for disease progression.

Other treatment options for PBC include the off-label use of fibrates. Bezafibrate (BZF) has not been approved for any indication in the US or any country for the treatment of patients with PBC, and a full clinical developmental program with BZF or any fibrate for the treatment of PBC has not been completed. However, fibrate treatment (including treatment with BZF) has been incorporated in various PBC treatment guidelines as an adjunctive therapy to UDCA for patients with PBC with an inadequate response to UDCA ([Lindor 2022](#), [EASL 2017](#)).

In a large retrospective cohort study of treatment effects in patients with PBC with an incomplete response to UDCA, the addition of BZF (a pan-peroxisome proliferator-activated receptor [PPAR] agonist) was associated with improved long-term liver transplantation-free survival (Tanaka 2021). Additionally, 2 clinical proof-of-concept studies have demonstrated that the combination of OCA and BZF had a strong, additive, beneficial effect on biomarkers of cholestasis in patients who had a sub-optimal response to second line therapies (Smets 2021, Soret 2021). Taken together, these studies suggest that OCA in combination with BZF has the potential for synergistic activity between farnesoid X receptor (FXR) and PPAR agonists. To address the urgent unmet need for effective PBC therapies, the Sponsor has initiated a development program with combination OCA and BZF to maximize the proportion of patients with PBC who rapidly achieve biochemical remission with a well-tolerated oral therapy.

5.2. Mechanism of Action of Obeticholic Acid and Bezafibrate

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

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

- Improvement in hepatic cholestasis with reduced inflammation and necrosis
- Prevention and reversal of hepatic stiffness

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

Fibrates exert potent anticholestatic effects through activation of PPAR α in hepatocytes as well as through downregulation of several pathways leading to bile acid synthesis (Ghonem 2015). BZF is a pan-PPAR (α , δ , γ) agonist approved in various locations outside the US that is indicated for primary and secondary hyperlipidemias. BZF causes a dose-dependent decrease in ALP in hyperlipidemia subjects. In PBC, subjects taking BZF showed a rapid and sustained decrease in ALP and a decrease in total bilirubin (Corpechot 2018).

At a 2019 American Association for the Study of Liver Diseases (AASLD) conference, evidence from clinical studies was presented indicating that BZF may also improve pruritus in patients with cholestatic liver diseases such as PBC and PSC (de Vries 2019).

5.3. Nonclinical Experience with Obeticholic Acid and Bezafibrate

5.3.1. Obeticholic Acid

A standard battery of nonclinical safety pharmacology and toxicology studies for OCA has been completed. No major nonclinical safety effects have been seen other than pharmacologic hepatic effects observed at high doses. These pharmacologic hepatic effects are consistent with the effects of a bile acid at exceedingly high hepatocellular exposure. Refer to the latest version of

the [OCA Investigator's Brochure](#) for additional information regarding the nonclinical program for OCA.

5.3.2. Bezafibrate

A standard battery of nonclinical safety pharmacology and toxicology studies for BZF has been completed. While hepatic tumor formation was observed in female rats with chronic administration of high doses of BZF, the dosage was approximately 30 to 40 times the human dosage. However, reduced intake levels more closely approximating the lipid-lowering dosage in humans showed no such effect. Refer to the latest version of the [Fixed Dose Combination \(FDC\) Investigator's Brochure](#) for additional information regarding the nonclinical program for BZF.

The Sponsor has completed a rodent combination toxicology study per International Conference on Harmonisation (ICH) guidance on nonclinical safety studies (ICH M3[R2]).

5.4. Clinical Experience with Obeticholic Acid and Bezafibrate

Study 747-214 will be the first Intercept-sponsored randomized, double-blind Phase 2 study conducted with OCA and BZF in combination in the United States. Another randomized, double-blind Phase 2 study with OCA and BZF in combination has been initiated outside of the United States (Study 747-213). Study 747-213 is assessing different BZF doses and formulations, including 200-mg immediate release (IR) tablets and 400-mg sustained release (SR) tablets in combination with OCA, using a 5-mg to 10-mg titration regimen. Several investigator-sponsored, proof-of-concept studies assessing the combination of OCA plus BZF for the treatment of PBC patients have been reported and are described in [Section 5.5.1](#).

5.4.1. Obeticholic Acid

As of 26 May 2023, since the commencement of the development program, approximately 4616 subjects (3549 patients and 1067 healthy volunteers) have received OCA in clinical studies sponsored by Intercept and Sumitomo Pharma Co., Ltd., (Intercept's former co-development partner in China, Korea, and Japan). The estimated cumulative patient exposure from marketing experience is 37,194 patient-years.

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

OCA (Ocaliva) has received marketing authorization in the US, Europe, and several other countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Per the Core Company Data Sheet (CCDS) v.4.0, Ocaliva is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event and in patients with complete biliary obstruction. In the US, per United States Prescribing Information (USPI),

Ocaliva is also contraindicated in patients with compensated cirrhosis with evidence of portal hypertension.

The PBC indication was approved based on a reduction in ALP. Data that supported approval of Ocaliva included 3 randomized, double-blind, placebo-controlled, multi-center, international studies in subjects with PBC:

- Study 747-201 was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in subjects with a proven or likely diagnosis of PBC who were suboptimally controlled. In this study, OCA doses of 10 mg and 50 mg were evaluated as monotherapies.
- Study 747-202 was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in subjects with a proven or likely diagnosis of PBC who were suboptimally controlled. OCA doses of 10 mg, 25 mg, and 50 mg were evaluated as add-on therapy to UDCA, the current standard of care for PBC.
- Study 747-301 was the pivotal Phase 3, 12-month, international, double-blind, placebo-controlled study in subjects with a proven or likely diagnosis of PBC who were suboptimally controlled. In this study, OCA doses evaluated were 10 mg or a titration approach (i.e., 5 mg for the initial 6 months, with uptitration to 10 mg for the last 6 months if the subject did not meet the primary composite endpoint and had no tolerability issues).

Each of these 3 studies included open-label, uncontrolled, LTSE phases to evaluate the long-term effects of OCA treatment. The LTSEs of Studies 747-201, 747-202, and 747-301 are completed.

An additional, 8-week, open-label study was also supportive of Ocaliva approval; however, efficacy data from this study was not integrated with Studies 747-201, 747-202, and 747-301 due to differences in study design and endpoints:

- Study 747-205 assessed the safety, tolerability, and PD effects of OCA on HDLc metabolism in subjects with PBC on a stable dose of UDCA. As of 26 May 2023, the LTSE phase is completed.

Completed postmarketing requirement studies in subjects with PBC included the following:

- Study 747-302 (postmarketing requirement) was a double-blind, randomized, placebo-controlled, multicenter study designed to prospectively obtain evidence to confirm clinical benefit and further evaluate the benefit-risk profile of OCA treatment in subjects with PBC.
- Study 747-401 (postmarketing requirement) was a double-blind, randomized, placebo-controlled study evaluating the PK and safety of OCA in subjects with PBC and moderate to severe hepatic impairment.

Enrollment in studies 747-302 and 747-401 was paused starting in early 2020 due to the COVID-19 pandemic and data monitoring committee (DMC) recommendations. Studies 747-401 and 747-302 were terminated in July 2021 and December 2021, respectively. Of note, neither of the studies were terminated for a safety reason.

Refer to the latest version of the [Ocaliva US Package Insert \(US Label\)](#) for additional information regarding OCA safety.

5.4.2. Bezafibrate

Although BZF is not licensed for treatment of subjects with PBC, both the AASLD and EASL guidelines for PBC mention the investigational or off-label use of fibrates for the treatment of PBC ([Lindor 2022](#), [EASL 2017](#)).

BZF is a low-solubility-high-permeability drug that is almost completely absorbed following oral administration. BZF is extensively bound to plasma proteins and is primarily eliminated in the urine as parent drug. Renal impairment significantly increases BZF systemic exposure and the coadministration of ion-exchange resins like cholestyramine with BZF significantly reduced the systemic exposure of BZF.

The literature contains various reports of fibrate monotherapy studied in the treatment of PBC, including a systematic review and meta-analysis of 9 clinical trials (total of 269 subjects) that evaluated the efficacy and safety of BZF mono-therapy treatment in subjects with PBC ([Yin 2015](#)) ([Appendix A](#)) (400 mg/day) for at least 8 weeks and up to 110 months. When added to background therapy with UDCA in subjects with PBC, BZF has demonstrated efficacy in a large randomized, blinded, placebo-controlled trial (BEZURSO). After 24-months of combined treatment (BZF 400 mg/day + UDCA), subjects treated with BZF + UDCA had a significantly higher rate of complete biochemical response (defined as normal levels of total bilirubin, ALP, aminotransferases, and albumin, and a normal prothrombin index) than subjects treated with placebo + UDCA (31% versus 0%) ([Corpechot 2018](#)). Overall, 424 adverse events (AEs) were reported in 88 subjects (49% in the BZF group and 51% in the placebo group) and a total of 39 SAEs were reported in 26 subjects (28% in the BZF group and 24% in the placebo group). The most frequently reported AEs were arthralgia and myalgia ([Corpechot 2018](#)).

In PBC subjects that are refractory to UDCA therapy, BZF (or fenofibrate) treatment is associated with a higher probability of ALP normalization and a lower risk of cirrhosis development and hepatic deterioration ([Chung 2019](#)). Furthermore, a retrospective analysis in 118 Japanese subjects who had received UDCA monotherapy for at least 1 year followed by combination therapy with UDCA + BZF for at least 1 year demonstrated improved GLOBE and UK-PBC scores and long-term prognosis of the PBC subjects ([Honda 2019](#)).

BZF therapy also has demonstrated benefit beyond improvements in liver function. Data on subjects who received BZF (400 mg/day) or placebo for a period of 21 days were presented. The primary endpoint was a 50% reduction of pruritus determined by visual analogue scale (VAS) score. Seventy subjects (37 BZF and 33 placebo), who had a VAS score >5 out of 10 at baseline, completed the study. A $\geq 50\%$ reduction of pruritus VAS was reported in 38% of subjects who received BZF ($n = 37$) compared with 12% of subjects who received placebo ($p = 0.03$). Subjects who were treated with BZF reported a reduction in the median morning ($p = 0.01$) and evening ($p < 0.01$) intensity of pruritus VAS when compared to placebo. Serum ALP decreased by 36% for subjects who received BZF, but not for placebo ($p = 0.04$); this correlated with a reduction of the VAS pruritus score ($p < 0.001$). Collectively, these data demonstrate that BZF is superior to placebo in improving pruritus in chronic cholestatic liver diseases such as PSC and PBC ([de Vries 2019](#)).

Across all studies, BZF appeared to be generally well tolerated and the AEs reported in subjects with PBC were mostly mild, affecting predominantly the gastrointestinal tract, skin, and musculoskeletal system. Impaired liver and kidney function have also been reported, albeit less frequently (<1%).

Refer to the latest version of the [FDC Investigator's Brochure](#) for additional information regarding clinical experience with BZF.

5.5. Rationale for Study Design and Dose for Investigational Products

5.5.1. Rationale for Combination Study Design

UDCA is widely accepted to be the first-line therapy for PBC. However, PBC may progress despite UDCA treatment, and some PBC subjects are unable to tolerate UDCA. The 2017 EASL guidelines indicate that subjects should continue to be evaluated for their risk of developing end-stage complications that may require treatments in addition to UDCA. For subjects who respond to UDCA, an individualized approach is recommended, while the addition of second-line therapy is recommended for subjects with an inadequate response to UDCA. Second-line therapy is specified as licensed OCA, off-label medications (e.g., fibrates, budesonide), and investigational treatments under evaluation in clinical trials ([EASL 2017](#)).

OCA is a selective FXR agonist that has been shown to affect significant reductions in ALP in subjects with PBC who demonstrated no or partial response to UDCA. As such, OCA has been conditionally approved for subjects with PBC in combination with UDCA for those with an inadequate response to UDCA or who are intolerant to UDCA.

Several small studies and non-randomized trials in PBC have suggested that fenofibrate or BZF in combination with UDCA may reduce ALP levels in non-or partial UDCA responders. In a recent prospective, double-blind randomized study, addition of 400 mg/day BZF in subject with PBC with inadequate biochemical response to UDCA was reported to improve pruritus, biochemical prognostic markers, and liver stiffness progression ([Corpechot 2018](#)). This study also provided important information concerning the safety profile of BZF when used longer term in subjects with PBC.

The existing clinical evidence in the published literature and complementary mechanisms of action of OCA and BZF suggests potential benefit for the PBC subjects on background UDCA therapy from the combination of OCA plus BZF compared with OCA or BZF alone. In a EASL 2019 presentation, the OCA, UDCA, and BZF combination efficacy, safety, and tolerability in 11 PBC subjects who had received OCA and UDCA for 5 years were described as follows: after 6 months of OCA, ALP decreased in 73% ($p < 0.001$) and bilirubin in 64% ($p = 0.625$) of the subjects. After 4 to 5 years (OCA mono-therapy registration study), none of the subjects reached the primary endpoint (normal ALP: 0/11 and normal bilirubin: 9/11). After 6 months of triple treatment, ALP further decreased in 100% ($p < 0.001$) and bilirubin in 67% ($p = 0.184$) of the subjects. ALP was normal in 4/9 and bilirubin in 8/9 of the subjects, reaching the primary endpoint in 44% of the subjects. Itching decreased in 5/7 of the subjects with BZF therapy and their mean PBC-40 score decreased from 6.0 to 4.6 points ($p = 0.070$). The conclusion of the authors was that combination therapy of OCA and BZF in subjects with PBC had a strong additive effect on cholestasis and improved pruritus ([Smets 2019](#), [Smets 2020](#)). The subsequent article defined the treatment algorithm in which these 11 POISE subjects, who were already on

UDCA (13-15 mg/kg/day) and OCA (5-10 mg/day), received add-on BZF (400 mg/day) for one year; triple therapy (TT). OCA was then withdrawn over 6 months irrespective of ALP normalization. Reintroduction of OCA occurred at the same baseline dose however, in those without increases in ALP levels, OCA was discontinued. Myalgia developed in 3/11 subjects within 2 weeks of TT: BZF was discontinued in one subject and dose reduced to 400 mg every 2 days in the other two subjects. A significant decrease in ALP after one year of TT was observed: ALP decreased in 9/10 subjects and normalized in 7/10 subjects, $p < 0.001$. A significant decrease in bilirubin levels $\leq 6 \times$ ULN was also observed in 8/10 subjects, $p < 0.01$. Using PBC-40, pruritus was reported in 8/11 subjects at baseline and after one year of TT. Using VAS score, 3/11 subjects reported mild pruritus and 4/11 subjects reported moderate pruritus at the beginning of therapy. After one year, 5 subjects reported no pruritus, 4 had mild pruritus, and one had moderate pruritus; mean VAS score decreased to 1.3 points (not significant). This study showed that the use of TT improved or normalized markers of cholestasis in most patients who failed to respond to UDCA and OCA dual therapy (Smets 2021).

A multicenter, retrospective cohort study investigated whether combination therapy of OCA (5-10 mg/day) and fibrates (BZF 200-400 mg/day or fenofibrate 100-200 mg/day), along with UDCA (13-15 mg/kg/day), had additive benefits in those with difficult-to-treat PBC. Fifty-eight subjects from 19 centers across 7 countries (France, Belgium, Italy, Germany, UK, Spain, and US) were included: mainly female of 50 years old; median ALP $2.7 \times$ ULN; pruritus in 59%; proven or predicted cirrhosis in 22%; median duration of prior UDCA therapy was 4.1 years (range 1.0-24.8); average UDCA dose was 15.4 (4.0) mg/kg/day (range 7.6-24.6); features of PBC-AIH overlap in 11 (19%) subjects (Soret 2021).

A total of 29 subjects (Group OCA-Fibrate) received OCA as second-line and fibrates as third-line therapies while 29 subjects (Group Fibrate-OCA) received fibrates as second-line and OCA as third-line therapies, in addition to UDCA. Between the two groups, a majority of subjects received BZF ($n = 47$) compared to fenofibrate ($n = 7$) while a small minority received both fibrates ($n = 4$). The mean (SD) duration of dual and TT was 2.8 (4.3) and 0.8 (0.6) years, respectively.

TT was associated with a significant reduction in ALP (primary endpoint) level compared to dual therapy: 22% per year (95% CI: 12%-31%; $p < 0.001$). When assessed by group, TT-associated reduction in ALP was significantly higher in Group OCA-Fibrate at 42% per year (95% CI: 29%-53%; $p < 0.001$) than Group Fibrate-OCA at 11% per year (95% CI: -3%-23%; $p = 0.1$); ALP reduction was seen as early as 3 months on TT. TT was associated with an odds ratio for ALP normalization of 3.4 per year (95% CI: 1.4-8.2; $p < 0.01$) as well as a significant decrease in total bilirubin ($p < 0.01$), GGT ($p < 0.001$), AST ($p < 0.01$), and ALT ($p < 0.001$) compared to dual therapy. The likelihood of achieving adequate biochemical response in TT was associated with an odds ratio of 6.8 per year (95% CI: 2.8-16.7; $p < 0.001$) for the Paris-2 criteria and 9.2 per year (95% CI: 3.4-25.1; $p < 0.001$) for the Toronto criteria. When assessed by group, the odds ratio remained higher in the OCA-Fibrate group at 12.7 per year (95% CI: 2.7-58.7; $p < 0.001$) for the Paris-2 criteria and 30.7 per year (95% CI: 4.7-199.6; $p < 0.001$) for the Toronto criteria. TT was associated with significant reduction in itch intensity score in Group OCA-Fibrate with a mean reduction of 72% per year (95% CI: 24%-90%; $p < 0.05$) but not in Group Fibrate-OCA. When pruritus was considered as a binary variable (absent vs. present), the odds ratio of no pruritus in

the entire population on triple therapy was 2.5 per year (95% CI: 0.9-6.9; $p=0.08$). Group OCA-Fibrate had an odds ratio of no pruritus at 9.9 per year (95% CI: 1.5-67.1; $p<0.05$) and was not significant in Group Fibrate-OCA. At the end of the study period, no subjects discontinued TT.

5.5.2. Rationale for Obeticholic Acid and Bezafibrate Doses and Duration

5.5.2.1. Obeticholic Acid

OCA studies in subjects with PBC (the “add-on” OCA study, Protocol 747-202, and the monotherapy study, Protocol 747-201) showed that 10 mg/day of OCA produced statistically significant and clinically meaningful reductions in ALP and other biochemical analytes. Doses higher than 10 mg were not more effective, but the incidence of pruritus was increased. The currently approved doses of OCA for PBC are 5 mg/day and 10 mg/day.

The DB Phase of this study is being conducted for 12 weeks (3 months). In the Phase 2 studies (747-201 and 202), the vast majority (>80%) of the ALP and liver enzyme reductions were evident after 1 month of therapy at the lower OCA dose (5 mg/day). Accordingly, this study will evaluate the 5 mg/day OCA dose in combination with BZF at two different doses (100 and 400 mg/day). All subjects in the combination group with BZF will start with OCA 5 mg once daily (once daily) on Day 1 and continue through the end of the DB Phase. Subjects who continue to meet protocol requirements will transition directly to the LTSE Phase upon completion of the Week 12 visit of the DB Phase. The end of the 12-week DB Phase becomes Day 1 of the LTSE Phase. All subjects transitioning into the LTSE Phase will receive treatment with OCA 5 mg once daily + BZF 400 mg once daily (Treatment D of the DB Phase) for the remainder of the study.

5.5.2.2. Bezafibrate

BZF is a pan-PPAR (α , δ , γ) agonist approved in multiple countries for the treatment of various primary and secondary hyperlipidemias. Standard dosages include the IR 200 mg tablet formulation administered up to 3 times daily (600 mg/day) or the SR 400 mg tablet formulation administered once daily (400 mg/day).

The BZF dose-response data were obtained from subjects with hyperlipidemia using triglycerides and/or cholesterol as response markers. The lowest available marketed BZF dosage is the 200 mg tablet. Based on the dose-response data from (Wolfram 1980), this dose would show less than maximal reductions in triglycerides and cholesterol in a hyperlipidemia population. For example, where a 400 mg/day BZF dose caused an estimated 18% reduction in triglycerides relative to placebo, a 200 mg/day dose caused a 9% reduction (Wolfram 1980). The doses of 200 and 400 mg/day BZF are currently being investigated in the Sponsor 747-213 study. The 9 studies that were reviewed (Yin 2015) and the controlled trial of BZF (Corpechot 2018) used BZF at a dosage of 400 mg/day, suggesting that this is the highest dose of interest, and thus will be used in the current study.

To better understand dose-response relationships, 100 mg and 400 mg are the daily doses of BZF being assessed in this study. Collectively between Studies 747-213 and 747-214, the Sponsor will evaluate BZF at 100, 200, and 400 mg/day, respectively, along with OCA at 5 mg/day only

and at 5 mg/day up-titrated to 10 mg/day, to establish the minimally effective and therapeutic doses.

A significant effect of BZF in combination with UDCA on ALP was seen as early as one month following initiation of treatment ([Akbar 2005](#)). Other studies have demonstrated that a significant effect was seen within 3 months of treatment ([Yin 2015](#)). Therefore, a 12-week DB Phase should be sufficient to see a significant change in ALP with the combination of OCA, BZF, and UDCA in up to 60 subjects with PBC.

5.6. Importance of Monitoring of Disease Progression

Given that PBC is a chronic, progressive liver disease, it is important that subjects with PBC are closely monitored to ensure early identification of potential disease progression to cirrhosis, hepatic decompensation, and/or hepatic injury. Extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to ensure subject oversight and safety. Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or hepatic decompensation coupled with rules-based laboratory monitoring as well as Investigator and Sponsor discretion.

As both drugs (OCA and BZF) are metabolized in the liver, it is important to monitor for potential hepatotoxicity through physical signs and symptoms, as well as laboratory testing of liver-related biochemical parameters. Subjects will be monitored for potential hepatic injury and/or hepatic decompensation and progression to cirrhosis ([Section 7.4](#)). Criteria for implementing dosing adjustments or discontinuations are described in [Section 7.6](#) and [Section 7.7](#), respectively.

5.7. Summary of Known Potential Benefits and Risks with Investigational Products

5.7.1. Benefits

The Sponsor plans to evaluate the combination of OCA + BZF for the treatment of PBC, including development of a to-be-marketed FDC product. There is a compelling rationale for the development of this combination as a treatment for PBC in that:

1. The efficacy and safety of BZF as second-line therapy in PBC has been evaluated in multiple clinical studies to date ([Agrawal 2019](#), [Feng 2019](#)),
2. Initial clinical proof-of-concept for the combination of OCA+ BZF has already been established ([D'Amato 2020](#), [Smets 2019](#), [Smets 2021](#), [Soret 2019](#), and [Soret 2021](#)). Two recent studies have demonstrated that the combined use of OCA + BZF on background therapy with UDCA may have additive clinical benefit in subjects with PBC compared with OCA or BZF alone ([Smets 2021](#), [Soret 2021](#)),
3. Many PBC subjects do not achieve response targets with currently available treatment options, indicating that combinatorial approaches to further improving clinical care are warranted. The combined use of OCA + BZF in PBC subjects has demonstrated

normalization of biomarkers of liver function (ALP and bilirubin) (Smets 2019, Corpechot 2019).

Several studies (approximately 610 subjects across greater than 20 studies) have suggested that BZF as second-line therapy may reduce ALP levels in PBC subjects who are non or partial UDCA responders (Agrawal 2019) (Appendix A). In a recently published Phase 3, randomized, double-blind, placebo-controlled study of treatment with BZF 400 mg/day for 24 months in 100 PBC subjects with an inadequate biochemical response to UDCA, BZF was reported to improve biochemical prognostic markers, liver stiffness progression, and pruritus (Corpechot 2018). This study also provided important information concerning the safety and tolerability profile of BZF when used long-term in subjects with PBC.

Based on these studies, fibrate treatment has recently been incorporated into various PBC treatment guidelines.

The AASLD guidance for the management of PBC states that fibrates can be considered as off-label alternatives for subjects with PBC and inadequate response to UDCA (Lindor 2019). Additionally, the current European Association for the Study of the Liver (EASL) guidelines for the management of PBC states that the off-label use of BZF may be an appropriate second-line therapy in subjects with an inadequate response to UDCA (EASL 2017). The existing clinical evidence in the published literature and the complementary mechanisms of action of OCA and BZF suggest OCA and BZF may have additive effects and thus potential benefit for PBC patients when used on background UDCA therapy (D'Amato 2020, Smets 2021, Soret 2019, Soret 2021).

Therefore, the Sponsor is conducting Study 747-214 as a Phase 2, randomized, double-blind, parallel-group study evaluating the efficacy, safety, and tolerability of OCA, administered in combination with BZF or BZF alone in subjects with PBC who had an inadequate response or who are unable to tolerate UDCA.

5.7.2. Risks

The known and potential risks of OCA and BZF are described in the FDC Investigator Brochure and are summarized in Table 1 and Table 2, respectively.

Table 1: Known and Potential Risks of OCA

OCA
Hepatic Adverse Events Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with OCA treatment in PBC patients with decompensated cirrhosis. OCA has not been adequately studied in patients with hepatic decompensation. Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dosage for that patient population; however, cases of hepatic decompensation and failure have continued to be reported in patients with decompensated cirrhosis even when they received the recommended dosage. Per the CCDS v.4.0, Ocaliva is contraindicated in patients with PBC with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event and in patients with complete biliary obstruction. In PBC patients with compensated cirrhosis, hepatic decompensation and failure have been reported. Some of these cases resulted in liver transplant. A dose-response relationship was observed for the occurrence of hepatic adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flares with dosages of OCA of 10 mg once daily to 50 mg once

OCA

daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with OCA in two 3-month placebo-controlled clinical trials in patients with primarily early stage PBC.

In a pooled analysis of three placebo-controlled clinical trials, in patients with primarily early stage PBC disease, the exposure-adjusted incidence rates for all serious and otherwise clinically significant hepatic adverse reactions, and isolated elevations in liver biochemical tests, per 100 PEY were: 5.2 in the OCA 10 mg group (highest recommended dosage), 19.8 in the OCA 25 mg group (2.5 times the highest recommended dosage) and 54.5 in the OCA 50 mg group (5 times the highest recommended dosage) compared to 2.4 in the placebo group.

Pruritus

The most commonly reported AE related to OCA is pruritus. Although pruritus has been observed in healthy volunteers and subjects with chronic liver disease, it most frequently occurs in subjects with PBC, which is not unexpected given that pruritus is a common symptom of chronic cholestatic diseases. In subjects with PBC, treatment with OCA at doses of 5, 10, 25, and 50 mg has been shown to cause a dose-dependent exacerbation of this common symptom. While the majority of pruritus events were mild and moderate in severity, severe pruritus was reported in 23% of subjects in the OCA 10 mg arm, 19% of subjects in the OCA titration arm, and 7% of subjects in the placebo arm in the pivotal Phase 3 study (747-301). In the subgroup of patients in the OCA titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from Months 0 to 6 and 15% from Months 6 to 12. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCA 10 mg, OCA titration, and placebo arms, respectively.

Lipid Profile Changes

Decreases in HDLc levels, which have been observed in subjects with PBC and NASH, were generally evident within 2 weeks of treatment commencement and trended back toward baseline with continued treatment. The clinical impact of the decrease in HDLc is unknown, especially for subjects with PBC in the context of their relative baseline elevated HDLc levels.

In subjects with PBC, a small but transient increase of LDLc levels was seen within 2 weeks of treatment commencement with OCA; however, mean LDLc levels in both OCA treatment arms in the pivotal Phase 3 study were almost identical with that observed in the placebo treatment arm by the end of the 52-week study. The clinical relevance of the treatment-emergent decrease in HDLc and modest and transient elevation in LDLc in this subject population is unknown and has not been shown to be associated with increased cardiovascular risk.

AE = adverse event; CCDS = Company Core Data Sheet; HDLc = high-density lipoprotein cholesterol; LDLc = low-density lipoprotein cholesterol; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PBC = primary biliary cholangitis; PEY = patient exposure years

Source: CCDS (on file) and [OCA Investigator's Brochure](#)

Investigators should ensure subjects are receiving OCA doses consistent with the protocol-specific dosing regimen and follow protocol-specific guidelines.

Table 2: Known and Potential Risks of BZF

BZF
Myositis and Rhabdomyolysis Treatment with drugs of the fibrate class including BZF has been associated on rare occasions with myositis or rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any subject with diffuse myalgias, muscle tenderness/weakness, or marked elevations in CK levels, and dose adjustment may be needed in patients with impaired renal function.
Liver Function Abnormal liver function tests have been observed occasionally during BZF administration, including elevated transaminases, and decreased or, rarely, increased alkaline phosphatase. However, these abnormalities are reversible upon discontinuation of the drug. Therefore, periodic liver function tests (AST, ALT, and GGT [if originally elevated]) in addition to other baseline tests are recommended after 3 to 6 months and at least yearly thereafter. BZF therapy should be terminated if drug related abnormalities persist.

BZF
Hepatobiliary Disease In patients with a past history of jaundice or hepatic disorder, BZF should be used with caution.
Cholelithiasis and/or Cholecystitis BZF may increase cholesterol excretion into the bile and may lead to cholelithiasis. Special attention should be given to the potential for cholelithiasis and/or cholecystitis.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BZF = bezafibrate; CK = creatine kinase; GGT = gamma glutamyl transferase; SmPC = Summary of Product Characteristics; SR = sustained release
Source: [Bezalip Mono 400 mg SR Tablets, SmPC 2016](#); [Bezafibrate 200 mg IR Tablets, Bezafibrate Retard 400 mg, SR Tablets, New Zealand Data Sheet. Teva Pharma \(New Zealand\) Limited \(2017\); SmPC 2016](#)

The overall safety profile of BZF is currently based on a combination of clinical study data and post-marketing experience in subjects with dyslipidemia, including severe hypertriglyceridaemia and mixed hyperlipidaemia. Decreased appetite and gastrointestinal disorders were the most common undesirable effects.

Clinical signs and symptoms of BZF overdose (apart from rhabdomyolysis) are unknown. In the case of overdose, BZF should be stopped, and appropriate symptomatic and supportive therapy should be administered as necessary. There is no specific antidote. Because BZF is highly bound to plasma proteins, hemodialysis should not be considered.

In cases of rhabdomyolysis, administration of BZF must be stopped immediately and renal function must be carefully monitored while rehydration is administered.

BZF may enhance the action of anticoagulants of the coumarin type. Therefore, the dose of the anticoagulant should be reduced by 30% to 50% at the start of treatment with BZF and then titrated according to the blood clotting parameters. Since some subjects are on anticoagulants and may develop a variceal bleed, special precaution should be taken to monitor and adjust their anticoagulant doses as needed. International normalized ratio (INR) is decreased following co-administration of warfarin and OCA. INR should be monitored and the dose of warfarin adjusted, if needed. Refer to the latest version of the [FDC Investigator's Brochure](#) for information regarding the BZF safety.

5.7.3. Considerations with the Use of OCA and BZF in Combination

There is currently no safety information from controlled trials using OCA and BZF in combination for the treatment of PBC. As both OCA and BZF are metabolized in the liver, it is important to monitor for potential hepatotoxicity through physical signs and symptoms, as well as laboratory testing of liver-related biochemical parameters. See [Section 7.4](#) for guidance on the monitoring and management of potential hepatic events and decompensation.

In considering use of OCA and BZF concomitantly, it is expected that the safety experience will be similar to the individual products. However, the overall safety profile of BZF is based on a different subject population and indication for the treatment of severe hypertriglyceridemia and mixed hyperlipidemia. Decreased appetite and gastrointestinal disorders were the most common undesirable effects. Cholelithiasis is a labeled undesirable effect of BZF (very rare) ([Bezalip Mono 400 mg Tablets, SmPC 2016](#), [Bezafibrate 200 mg Tablets, SmPC 2016](#)) and has also been reported in clinical studies at higher OCA doses in subjects with NASH. [Section 7.5](#)

provides detailed guidelines for the medical management of subjects with symptomatic cholelithiasis and/or cholecystitis.

Treatment with drugs of the fibrate class including BZF has been associated on rare occasions with myositis or rhabdomyolysis. Myopathy should be considered in any subject with diffuse myalgias, muscle tenderness/weakness, or marked elevations in creatine phosphokinase levels, and dose adjustment may be needed in subjects with impaired renal function. Subjects should be advised to report unexplained muscle pain, tenderness or weakness promptly, particularly if accompanied by malaise or fever. Creatine kinase (CK) levels should be assessed in subjects reporting these symptoms, and BZF therapy should be discontinued if markedly elevated CK levels (5x ULN) occur or myopathy is diagnosed. [Section 7.4.4.3](#) provides detailed guidelines for evaluating and monitoring subjects with potential myopathy. In cases of rhabdomyolysis, administration of BZF must be stopped immediately and renal function must be carefully monitored while rehydration is administered.

It is anticipated that the benefit risk profile of OCA + BZF used in combination will be positive.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective is to assess the effects of the combination of OCA and BZF on ALP in comparison to BZF alone in subjects with PBC.

6.2. Secondary Objectives

The secondary objectives are to assess the effects of the combination of OCA plus BZF versus BZF alone in subjects with PBC on the following:

- Biochemical disease markers, including ALP, GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
- Biomarkers of bile acid synthesis and homeostasis, including 7 α -hydroxy-4-cholesten-3-one (C4) and bile acids
- Safety and tolerability

6.3. Additional Objectives

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

7.1.1. Methodology

Overview: This Phase 2a, randomized, DB, active-controlled, parallel-group study will evaluate the efficacy, safety, and tolerability of OCA (5 mg/day) administered in combination with 2 different BZF doses (100 and 400 mg/day) compared to BZF alone (at 2 doses, 100 and 400 mg/day) in up to 60 subjects with PBC over at least 12 weeks.

Screening Phase (2 and up to 8 Weeks): Subjects will be screened for a period of up to 8-weeks before being randomized into the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) for verification of inclusion/exclusion criteria and to establish baseline (including Day 1).

Double-Blind Phase (12 Weeks): Subjects who meet the entry requirements will be randomized in a 1:1:1:1 ratio on Day 1 to receive either Treatment A (BZF 100 mg immediate-release [IR] once daily); Treatment B (BZF 400 mg IR once daily); Treatment C (OCA 5 mg once daily + BZF 100 mg IR once daily); or Treatment D (OCA 5 mg once daily + BZF 400 mg IR once daily). The DB Phase will be from Day 1 through Week 12; eligible subjects will then continue into the LTSE Phase through the end of the study.

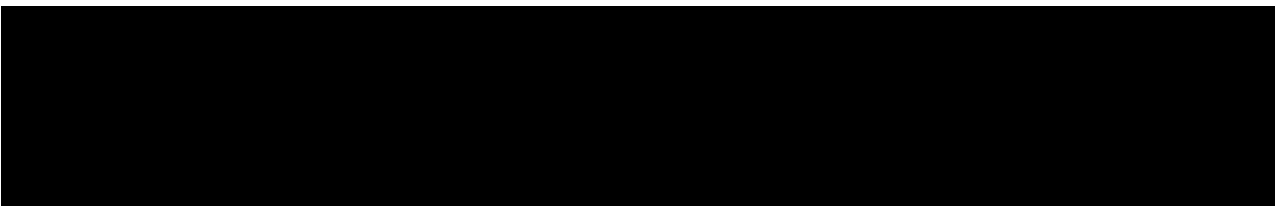
Once a subject is scheduled to be enrolled, the clinical site will inform the unblinded statistician via secured and restricted email (unblindedstats@interceptpharma.com) at least 3 to 4 days prior to dosing. The unblinded statistician will allocate the first 3 subjects in each treatment arm to PM dosing and will send an email to the site to provide dosing time (i.e., AM or PM). The Interactive Response Technology (IRT) system will notify the unblinded statistician by an auto-

generated alert after the first 3 subjects in one treatment arm are randomized. All subsequent subjects in the same treatment arm will be allocated to AM dosing (see [Section 9.4.1](#)). The unblinded statistician responsible for randomization will not be involved in the regular study operations and will have no communication with study team members or be involved in the interim analyses.

Investigational products will be taken orally once daily for the duration of the study. Subjects assigned to AM dosing will be instructed to begin dosing on Day 1 and to take investigational product between 7 AM-11 AM each day. Subjects assigned to PM dosing will take investigational product between 2 PM-5 PM for the entire DB Phase. After the completion of the DB Phase, all subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits).

Subjects must be instructed to swallow the tablets whole; investigational product must not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout study conduct.

After the Day 1 Visit, subsequent study visits during the DB Phase will occur at approximately Weeks 2, 4, 6, 8, 10, and 12 (Day 1 of LTSE) for the assessment of efficacy, safety, tolerability, and PK. These visits will also allow for the assessment of any AEs, changes to concomitant medications and/or new medications that have been initiated, medical/surgical procedures, and to verify that the subject is dosing as directed. A rolling evaluation of available efficacy and safety data may occur periodically during the DB Phase (see [Section 16.7](#)).



To preserve the study blind, appearance-matched placebo tablets for OCA and/or BZF will be administered to subjects in each treatment group as shown in [Figure 1](#) during the DB treatment phase.

Randomization will be stratified at baseline by the following:

- Total bilirubin levels ($\leq 0.7\times$ or $> 0.7\times$ ULN but $< 2\times$ ULN). This stratification is to ensure a balance of baseline disease severity between treatment arms ([Lammers 2014](#))

Studies examining OCA in subjects with PBC demonstrate OCA's underlying efficacy occurring at $ALP \geq 1.67\times$ ULN. The efficacy profile observed at this ALP level in the 12-month DB Phase 3 study in subjects treated with OCA remained durable over approximately 3 to 5 years of the long-term extension phase ([Nevens 2019](#), [Trauner 2019](#)). Conversely, in subjects with PBC treated with BZF from the BEZURSO study over a 24-month period had a baseline ALP entry-criteria of $\geq 1.5\times$ ULN ([Corpechot 2018](#)).

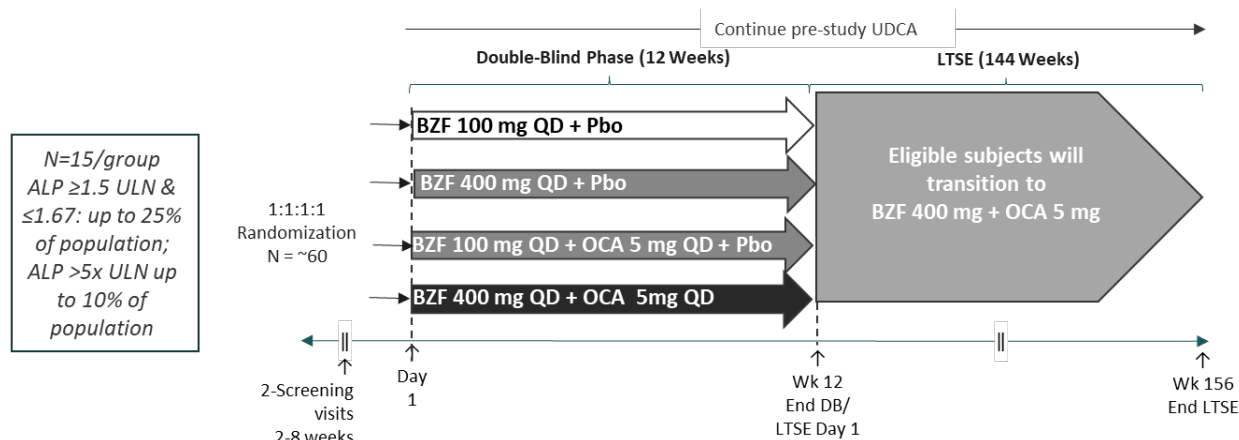
Randomization will therefore also be stratified by ALP at baseline by the following:

- $ALP (\geq 1.5\times$ ULN but $\leq 1.67\times$ ULN or $> 1.67\times$ ULN)
- $ALP > 1.67\times$ ULN (remaining subjects enrolled)

The percentage of subjects with baseline ALP ≥ 1.5 x ULN but ≤ 1.67 x ULN will not exceed 25% and the percentage of subjects with baseline ALP > 5 x ULN will not exceed 10%.

LTSE Phase (144 Weeks): Subjects who continue to meet protocol requirements will transition directly to the LTSE Phase (an open-label design) upon completion of the Week 12 visit of the DB Phase. The end of the 12-week DB Phase becomes Day 1 of the LTSE Phase. All subjects transitioning into the LTSE Phase will receive treatment with OCA 5 mg once daily + BZF 400 mg IR once daily (Treatment D of the DB Phase). Subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits).

Figure 1: Study Design for the Double-Blind and LTSE Phases (Study 747-214)



ALP = alkaline phosphatase; BZF = bezafibrate; DB = double blind; LTSE = long-term safety extension; OCA = obeticholic acid; Pbo = placebo; QD = once daily; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; Wk = week

Note: First 3 subjects per treatment group will be assigned to PM dosing.

Note: Placebo = either OCA or BZF tablets.

Note: Subjects taking UDCA at the time of enrollment will remain on their stable dose of UDCA during the study.

Note: LTSE Day 1 will be the last visit in the DB Phase (Week 12).

Note: Subjects that transition to the LTSE Phase will receive OCA 5 mg + BZF 400 mg IR QD.

7.1.2. Schedule of Study Procedures

Table 3: Schedule of Study Procedures During the DB Phase

	Screening Phase ^a			Double-Blind Phase							
	Screening Visit 1	Screening Visit 2	Day -4 to -3	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 (LTSE Day 1) ^w	ET ^b
Visit Window (Relative to Visit Day)	2 weeks to maximum of 8 weeks				±5 days	±5 days	±5 days	±5 days	±5 days	±2 weeks	
Fast ≥8 Hours Prior to Visit ^c		X		X	X	X	X	X	X	X	
Informed Consent Form	X										
Medical/ Surgical History and PBC History/ Demographics	X	X		X							
Prior and Concomitant Medications ^d	X	X		X	X	X	X	X	X	X	X
Myopathy Evaluation and Monitoring ^e	X	X		X	X	X	X	X	X	X	X
Inclusion/ Exclusion Criteria	X	X		X							
Physical Examination	X			X						X	X
Height	X										X
Weight (including BMI and waist-hip ratio) ^f	X	X		X	X	X	X	X	X	X	X
Vital Signs ^g	X	X		X	X	X	X	X	X	X	X
12-Lead ECG	X									X	X
AEs ^h	X	X		X	X	X	X	X	X	X	X
Ultrasound exam (RUQ) (cholelithiasis and gallbladder disease)	X										
CP Assessment ⁱ	X	X		X	X	X	X	X	X	X	X
MRS	X	X		X	X	X	X	X	X	X	X
Email Unblinded Statistician ^v			X								
Randomization/Treatment Assignment				X							

	Screening Phase ^a			Double-Blind Phase							
	Screening Visit 1	Screening Visit 2	Day -4 to -3	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 (LTSE Day 1) ^w	ET ^b
Visit Window (Relative to Visit Day)	2 weeks to maximum of 8 weeks				±5 days	±5 days	±5 days	±5 days	±5 days	±2 weeks	
Administer IP ^u				X	X	X	X	X	X	X	X
Dispense IP				X		X		X		X	
Administer Low-fat Meal or Meal Replacement Drink ^t						X					
Assess IP Accountability and Compliance					X	X	X	X	X	X	X
Serum Chemistry, Hematology, Coagulation ^m (including CK)	X	X		X	X	X	X	X	X	X	X
Thyroid Hormones (Free T3, free T4, and TSH)	X									X	X
Virology (HCV/hBsAg)	X										
Urinalysis	X	X		X	X	X	X	X	X	X	X
Urine-Based β-hCG Pregnancy Test ^o	X	X		X	X	X	X	X	X	X	X
Autoimmune liver disease panel (ANA, anti-smooth muscle antibody, anti-actin antibody)	X										

	Screening Phase ^a			Double-Blind Phase							ET ^b
	Screening Visit 1	Screening Visit 2	Day -4 to -3	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 (LTSE Day 1) ^w	
Visit Window (Relative to Visit Day)	2 weeks to maximum of 8 weeks				±5 days	±5 days	±5 days	±5 days	±5 days	±2 weeks	

Note: Unscheduled visits should occur as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered. AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [REDACTED]; AST = aspartate aminotransferase; β -hCG = beta-human chorionic gonadotropin; BMI = body mass index; BZF = bezafibrate; C4 = 7 α -hydroxy4-cholesten-3-one; C_{max} = peak (maximum) plasma concentration; CP = Child-Pugh; CK=creatinine kinase; DB = double-blind; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; [REDACTED]; [REDACTED] ET = early termination; [REDACTED]; GGT = gamma-glutamyl transferase; hBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IP = investigational products: OCA, BZF, and placebo BZF; MRS = Mayo Risk Score; [REDACTED]; OCA = obeticholic acid; PI=Principal Investigator; [REDACTED]; RUQ= right upper quadrant; T3 = triiodothyronine; T4 = thyroxine; [REDACTED]; TSH = thyroid-stimulating hormone; UDCA = ursodeoxycholic acid; [REDACTED]

- ^a The 2 Screening Visits must occur at least 2 weeks apart to confirm pretreatment serum chemistry levels, including ALT and AST. Day 1 cannot occur until confirmation of serum chemistry levels.
- ^b An ET visit should occur in subjects who withdraw from investigational product or withdraw consent during the DB Phase. The visit should be completed as near as possible to the subject's last dose of IP. See [Section 9.7.6](#) for additional instructions.
- ^c Subjects should be instructed to fast overnight (at least 8 hours) before Screening Visit 2 and all subsequent study visits, but water is permitted. Record fasting status in the source and eCRF. If the subject reports having eaten or drunk anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits. Remind subject to maintain either AM or PM dosing (Weeks 2, 4, 6, 8, 10, and 12). See [Section 9.7.4](#), [Section 9.7.5](#) for additional instructions.
- ^d Prior medications taken within 30 days of Day 1 are to be recorded at Screening and Day 1 only. For all other visits, only concomitant medications are to be recorded.
- ^e At Screening: check baseline (creatinine kinase) CK: If $\geq 5 \times$ ULN then screen fail. Check for previous history of myalgia: Yes or No. If Yes, rate on a scale of 1 to 10 with 1 being the least amount of discomfort and 10 being the most amount of discomfort to establish baseline. If subjects develop myopathy at any point during the study, CK values must be checked. A CK $\geq 5 \times$ ULN will require investigational product interruption. Laboratory values including CK and creatinine will be closely monitored every 2 weeks until values return to baseline levels.
- ^f Waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurement.
- ^g Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting for 3 minutes.
- ^h AE data will be collected from the time that signed informed consent is obtained until the subject fully completes her/his participation in the study.
- ⁱ CP Score will be calculated based on central laboratory evaluations and a targeted assessment of ascites and hepatic encephalopathy. Scores will be calculated by the Sponsor and recorded on the eCRF.
- ^j [REDACTED]
- ^k [REDACTED]
- ^l [REDACTED]
- ^m To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel.
- ⁿ At screening, a separate ICF will be used to obtain the subject's consent for the utilization of their [REDACTED] Sample can be taken at Screening or Day 1 and will be analyzed if needed.
- ^o Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the subject may not continue in the study taking IP. (Additional testing may be conducted where required, regionally). The subject is encouraged to continue scheduled visit until they complete the treatment phase.

P To be performed only if test is available at sites

- ^v Once a subject is scheduled to be enrolled, the clinical site will inform the unblinded statistician via secured and restricted email (**unblindedstats@interceptpharma.com**) at least 3 to 4 days prior to dosing. The unblinded statistician will allocate the subject to either AM or PM dosing and will send an email to the site to provide dosing time (i.e., AM or PM).
- ^w Continuation of Schedule of Study Procedures for LTSE shown in [Table 4](#).

Table 4: Schedule of Study Procedures During the LTSE Phase

	Long-Term Safety Extension Phase														
	Week 16	Week 20 ^p	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156 (EOS)	Unscheduled Visit ^s
	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	
STUDY PROCEDURES															
Fast ≥8 Hours Prior to Visit ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Myopathy Evaluation and Monitoring ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X	X
Weight (including BMI and waist-hip ratio) ^c	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs ^d	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG														X	X
AEs ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CP Assessment ^f	X		X	X	X	X	X	X	X	X	X	X	X	X	X
MRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer IP ^j	X		X	X	X	X	X	X	X	X	X	X	X		X

	Long-Term Safety Extension Phase														
	Week 16	Week 20 ^P	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 108	Week 120	Week 132	Week 144	Week 156 (EOS)	Unscheduled Visits ^S
	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	
Dispense IP	X		X	X	X	X	X	X	X	X	X	X	X		
Assess IP Accountability and Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLINICAL AND LABORATORY EVALUATIONS															
Serum Chemistry, Hematology, Coagulation ^k (including CK ^q)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid Hormones (Free T3, free T4, and TSH)	X			X		X		X		X		X		X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine-Based β-hCG Pregnancy Test ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: LTSE Week 156 is the last visit in the LTSE Phase and is the EOS. If a subject discontinues treatment or discontinues the study before LTSE Week 156, they undergo the EOS Visit which will be their final visit. LTSE Week 156 and EOS have the same assessments required.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [REDACTED] AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BMI = body mass index; BZF = bezafibrate; [REDACTED] CK=creatinine kinase; CP = Child-Pugh; DB = double-blind; ECG = electrocardiogram; eCRF = electronic case report form; EDC = electronic data capture; eGFR = estimated glomerular filtration rate; [REDACTED] ET = early termination; [REDACTED] GGT = gamma-glutamyl transferase; IP = investigational products; OCA, BZF, and placebo BZF; LTSE = long term safety extension; [REDACTED] MRS = Mayo Risk Score; [REDACTED];

OCA = obeticholic acid; PI = Principal Investigator; [REDACTED]; T3 = triiodothyronine; T4 = thyroxine; [REDACTED]; TSH = thyroid-stimulating hormone; UDCA = ursodeoxycholic acid; [REDACTED]; ULN = upper limit of normal; VAS = visual analog scale

- ^a Subjects should be instructed to fast overnight (at least 8 hours) before all study visits, but water is permitted. Record fasting status in the source and eCRF. If the subject reports having eaten or drunk anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits. See [Section 9.7.4](#), [Section 9.7.5](#) for additional instructions.
 - ^b If subjects develop myopathy at any point during the study, CK values must be checked. A CK ≥ 5 x ULN will require investigational product interruption. Laboratory values including CK and creatinine will be closely monitored every 2 weeks until values return to baseline levels.
 - ^c Waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurement.
 - ^d Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting for 3 minutes.
 - ^e AE data will be collected from the time that signed informed consent is obtained until the subject fully completes her/his participation in the study.
 - ^f CP Score will be calculated based on central laboratory evaluations and a targeted assessment of ascites and hepatic encephalopathy. Scores will be calculated by the Sponsor and recorded on the eCRF.
 - ^g [REDACTED]
 - ^h [REDACTED]
 - ⁱ [REDACTED]
 - ^j At each study visit, the daily dose of investigational product should be administered at the site for subjects allocated to AM dosing. All assessments must be completed before administration of investigational product and UDCA (if applicable).
 - ^k To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel.
 - ^l Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the subject may not continue in the study taking IP. (Additional testing may be conducted where required, regionally). The subject is encouraged to continue scheduled visit until they complete the treatment phase.
 - ^m To be performed only if test is available at sites.
 - ⁿ [REDACTED]
 - ^o Blood samples will be collected at predose of cholate and 5, 20, 45, 60, and 90 minutes after administration of stable label cholate.
 - ^p This visit will include laboratory evaluations as indicated, but the remainder of the information will be collected via a phone call.
 - ^q Subjects who are transitioned from a different dose to the respective transition dose will be monitored with safety labs (liver biochemistries and CK levels) at 4 weeks after the transition, and if not significantly changed, then every 4 weeks until 12 weeks after the transition, at which point safety labs will be done every 3 months (unless there are significant changes in the labs which would be handled per protocol).
- [REDACTED]

7.1.3. Study Duration

The total duration of the study per subject will be a DB duration of 12 weeks and LTSE up to 144 weeks. Subjects who continue to meet protocol requirements will transition directly into the LTSE Phase once they complete the 12-week DB Phase.

7.2. Number of Subjects

Up to 60 subjects (15 per group) will be enrolled and randomized in a 1:1:1:1 ratio to 1 of 4 treatment arms (Treatments A, B, C, or D).

7.3. Planned Dosing Regimen

Subjects will be randomly assigned in a 1:1:1:1 ratio to receive one of the following treatments during the 12-week DB Phase:

<u>Treatment A:</u> BZF 100 mg IR tablet once daily	OCA placebo tablet BZF 100 mg IR tablet BZF placebo tablet
<u>Treatment B:</u> BZF 400 mg IR tablet once daily	OCA placebo tablet BZF 200 mg IR tablet BZF 200 mg IR tablet
<u>Treatment C:</u> OCA 5 mg once daily + BZF 100 mg IR once daily	OCA 5 mg tablet BZF 100 mg IR tablet BZF placebo tablet
<u>Treatment D:</u> OCA 5 mg once daily + BZF 400 mg IR once daily	OCA 5 mg tablet BZF 200 mg IR tablet BZF 200 mg IR tablet

BZF = bezafibrate; IR = immediate release; OCA = obeticholic acid

Subjects who continue to meet protocol requirements will transition directly to the LTSE Phase upon completion of the Week 12 visit of the DB Phase. All subjects who transition to the LTSE Phase will receive the OCA 5 mg once daily + BZF 400 mg IR once daily dose (same as Treatment D of the DB Phase). For dosing instructions refer to [Section 11.2.2](#).

7.4. Monitoring and Management of Potential Muscular or Hepatic Injury and/or Disease Progression

Given the chronic and progressive nature of PBC, it is important to monitor for potential hepatic injury, disease progression, and/or hepatic decompensation. Child-Pugh (CP) and [REDACTED] will be reviewed at each visit where labs are collected ([Section 7.4.4](#) and [Section 15.2.1](#)). CP Scores will be assessed in all subjects regardless of evidence of cirrhosis. In addition, AEs, signs and symptoms of potential hepatic injury or hepatic decompensation, and laboratory values will also be reviewed at regular intervals as described in [Section 7.1.2](#). Based on the assessments of signs and symptoms of hepatic injury and liver biochemistry ([Section 7.4.1](#)), the investigational product (OCA or BZF) may be interrupted or discontinued per the criteria discussed in [Section 7.4.2](#) and [Section 7.4.3](#).

7.4.1. Signs and Symptoms of Hepatic Injury or Hepatic Decompensation

Subjects should be instructed to contact study personnel immediately if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting:

- Specific signs and symptoms of liver impairment: e.g., yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber (dark) (reflecting impaired bilirubin metabolism)
- More general signs and symptoms of ascites and encephalopathy: e.g., confusion, swelling of the legs or abdomen
- Non-specific signs and symptoms of impaired health: e.g., nausea, vomiting, abdominal pain, diarrhea, weight loss, fever, chills, worsening or new fatigue, weakness, loss of appetite
- Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or hepatic decompensation (e.g., established severe abdominal pain, vomiting, and persistent diarrhea) and should be an indication for prompt investigational product interruption and complete subject evaluation.

Other Symptoms:

- Worsening of renal function (e.g., reduced urine output) or likely dehydration
- New or worsening baseline myalgias or likely myositis

Healthcare Provider (HCP) Interactions:

- Visits to primary HCP or referral to any specialist for any new symptoms (other than ongoing care for stable comorbidities)
- New medications or changes to current medications prescribed from HCP or any new over the counter medications or herbal supplements
- Laboratory procedures or assessments performed by an HCP

Signs and symptoms for potential hepatic injury or hepatic decompensation should be followed by (1) evaluation of liver biochemistry for suspected drug-induced liver injury (DILI) or potential hepatic decompensation, (2) assessment of clinical events for potential hepatic decompensation ([Section 7.4.2](#)), (3) triggering of investigational product interruption or discontinuation per criteria ([Section 8.2.1](#)), (4) documentation in the AE eCRF or the SAE eCRFs ([Section 15.1.5.1](#) and [Section 15.1.5.2](#)), and (5) contact with the Medical Monitor ([Section 15.1.5.2](#)).

7.4.2. Assessments for Suspected Hepatic and/or Muscular Injury or Potential Hepatic Decompensation

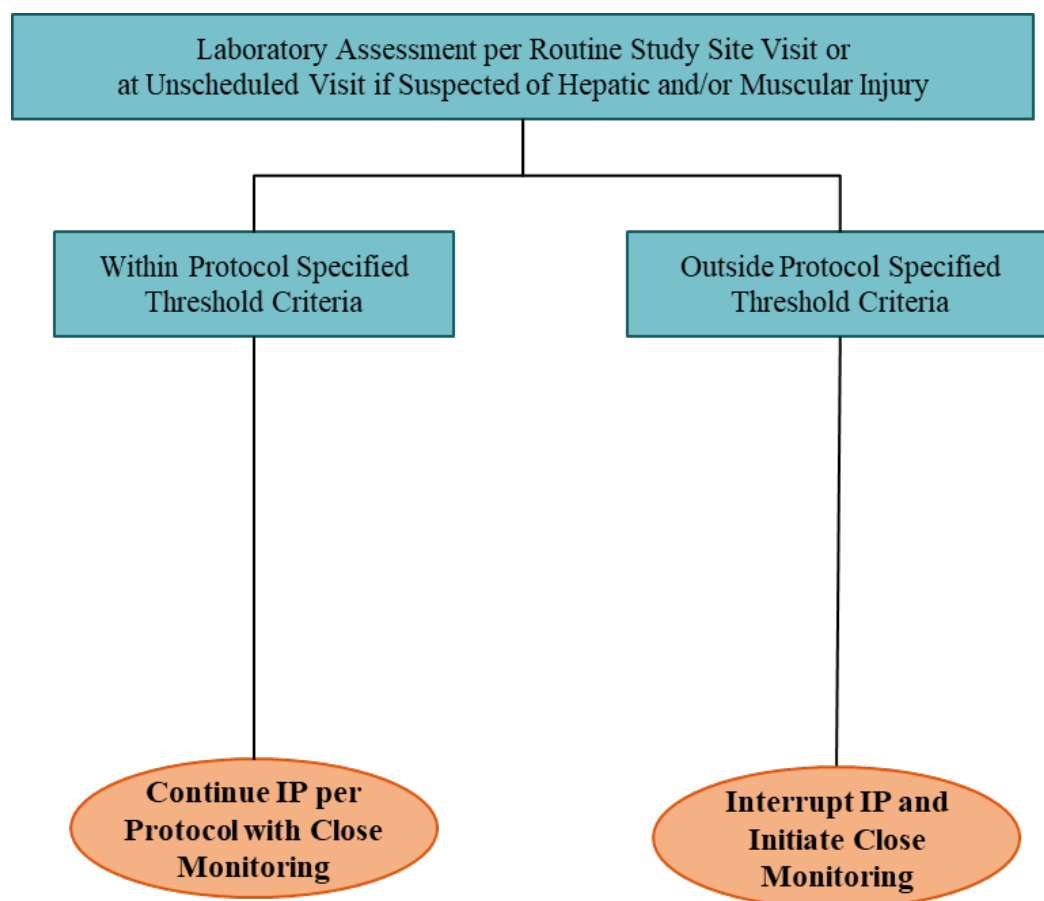
Liver biochemistry and serum CK will be assessed to evaluate for potential hepatic and/or muscular injury or hepatic decompensation. These assessments will be performed at:

- Each protocol-specified visit ([Table 3](#) and [Table 4](#))
- Unscheduled visits as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered

It is important that the laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. In the event that a subject cannot complete a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local lab is permissible at the discretion of the Investigator. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges.

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and potentially a complete subject evaluation (depending on the repeat result) are summarized in [Table 5](#).

Figure 2: Management Algorithm for Suspected DILI and/or Muscular Injury



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK=creatinine kinase; DILI = drug-induced liver injury; GGT = gamma-glutamyl transferase; INR = international normalized ratio; IP = Investigational Product; PK = pharmacokinetic

Laboratory assessments include: ALT, ALP, AST, GGT, direct and total bilirubin, INR, and CK.

Note: [REDACTED]; close monitoring including physical exams and repeat biochemistry labs should occur as often as deemed appropriate by the Investigator (see [Table 5](#)).

Table 5: Laboratory Criteria for Monitoring of Suspected Hepatic and Muscular Injury and Interruption^a of Investigational Product

Baseline ^b	Treatment Emergent	Liver Signs and Symptoms ^c
Any value	Any hepatic enzyme elevation (TB, ALP, AST, ALT, GGT)	Y
ALT or AST Normal	ALT or AST ≥ 3 x ULN and TB ≥ 2 x BL	Y or N
	ALT or AST ≥ 3 x ULN and INR > 1.5	Y or N
	ALT or AST ≥ 5 x ULN and Any TB	Y or N
ALT or AST Elevated	ALT or AST ≥ 2 x BL and TB ≥ 2 x BL	Y or N
	ALT or AST ≥ 2 x BL and INR > 1.5	Y or N
	ALT or AST ≥ 3 x BL (or ≥ 300 , whichever first) and Any TB	Y or N
TB $\leq$ ULN	TB ≥ 2 x BL and $>$ ULN	Y or N
TB $>$ ULN	TB ≥ 1.5 x BL or ≥ 3.0 mg/dL, whichever occurs first	Y or N
ALP $\leq$ ULN	ALP ≥ 2 x BL and $>$ ULN	Y or N
ALP $>$ ULN	ALP ≥ 2 x BL or ≥ 1000 U/L, whichever occurs first	Y or N
CK	≥ 5 x ULN or ≥ 3 x ULN with symptoms of rhabdomyolysis ^{d,e}	N/A

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = direct bilirubin; RUQ = right upper quadrant; TB = total bilirubin; ULN = upper limit of normal

^a Interrupt study drug; Initiate workup of competing etiologies and close monitoring (repeat labs and exam 2-3 times per week), including repeat labs initially.

- Study drug can be restarted after a minimum of 30 days if another etiology is identified, liver enzymes return to baseline, lab abnormalities are determined not to be due to DILI, no symptoms, and approved by the Medical Monitor and Investigator.
- If study drug is restarted after 30 days, repeat labs in 2-5 days for ALT, AST, and TB or 7-10 days for ALP as indicated and continue close monitoring.

^b New baseline values for DILI monitoring for ALT, AST, ALP, TB should be determined based upon average of month 3 and 6 values if average is $>50\%$ decrease from original baseline. Adapted from [Palmer 2020](#).

^c Liver signs and symptoms to include: new onset of severe fatigue or significant worsening of baseline fatigue; new onset of severe pruritus or significant worsening of baseline pruritus; nausea, vomiting, RUQ pain; fever, rash, or $>5\%$ eosinophilia; new onset of hepatic decompensation (e.g., ascites, variceal bleeding, hepatic encephalopathy).

^d Symptoms of rhabdomyolysis may include muscle swelling; weak, tender, sore muscles; dark urine; fever; tachycardia; nausea and vomiting; confusion; dehydration; abdominal pain.

^e If investigational product interrupted due to CK trigger, ensure follow CK and creatinine/renal function in addition to liver biochemistries with close monitoring as above; same criteria apply to considering re-initiation of investigational product.

It should be noted that it is difficult to recognize every potential marker of marker of hepatic deterioration or muscular injury. There is no substitute for good medical judgment.

Investigators will be reminded to be cautious and mindful in their evaluation of subjects' symptoms, signs, and laboratory results. However, for example, a single abnormal laboratory analyte result may be artifactual; accordingly, Investigators will be allowed to implement an alternate follow-up procedure if considered appropriate based on their medical judgement but only after documented agreement with the Sponsor's Medical Monitor.

7.4.3. Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events

Subjects will be monitored for potential hepatic decompensation events throughout the study. Investigational product is to be permanently discontinued with the development of any clinical events listed in [Table 6](#).

Subjects who experience hepatic decompensation events should be closely monitored until normalization or stabilization using good clinical judgement, and, per Food and Drug Administration (FDA) guidance for observation of potential DILI, should include, but not be limited to, a thorough clinical evaluation including repeat liver enzymes and tests of liver function two to three times weekly with subsequent frequency to be determined by clinical status; complete history and physical; evaluation of concomitant drugs, alcohol, illicit drug use; concomitant liver conditions including viral hepatitis; environmental exposures; consider gastroenterology or hepatology consultation.

After stabilization, subjects should continue with scheduled study visits for safety follow up. During the DB and LTSE Phase, monitoring will occur on a bi-monthly basis from Day 1. Subjects who experience a decompensation event during the DB Phase will not be eligible to enroll in the LTSE Phase.

Table 6: Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Mandatory Discontinuation of Investigational Product

- Evidence of portal hypertension (e.g. platelet count <150,000/ μ L, splenomegaly, presence of varices)
- Liver Transplant, under evaluation for liver transplant, or listed for transplant
- Progression to CP score ≥ 7
- New onset of any of the following:
 - Ascites
 - Hepatic hydrothorax
 - Hepatic encephalopathy – requires hospitalization and/or lactulose and/or rifaximin
 - Variceal bleeding
 - Jaundice (with total bilirubin >3 mg/dL [$>51.3 \mu\text{mol/L}$])
 - [REDACTED]
 - Hepatocellular carcinoma (HCC)
- Any liver-related event requiring hospitalization and treatment
- Hepatorenal syndrome Type 1 or Type 2, hepatopulmonary syndrome, or portopulmonary syndrome

CP = Child-Pugh; HCC = hepatocellular carcinoma; [REDACTED]

7.4.4. Child-Pugh Score

Child-Pugh (CP) Score ([Pugh 1973](#), [Lucey 1997](#)) is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF by adding the scores from the 5 factors outlined in [Table 7](#) and can range from 5 to 15. CP score calculation will automatically be computed in all subjects (at all times data are obtained for the eCRF). Dose adjustment or discontinuation should not be considered based solely on the CP score in subjects who do not meet criteria for presence of cirrhosis.

A total score of 5 to 6 is considered Class A; a score of 7 to 9 is Class B (moderate, significant functional compromise); and a score of 10 and above is Class C (severe, decompensated disease). The Sponsor calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the AE review at the scheduled

visits, as well as total bilirubin, serum albumin, and prothrombin time (PT), the data for which will be obtained from the central laboratory.

Table 7: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	μmol/L	<34	34-50	>50
	mg/Dl	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	28-35	<28
	g/Dl	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites	N/A	None	Mild	Moderate-Severe
Hepatic encephalopathy ^a	N/A	No	Grade 1 or 2	Grade 3 or 4

CP = Child-Pugh; CPS = cycles per second; INR = international normalized ratio

The CP score is calculated by adding the scores for the 5 factors and can range from 5-15. CP class is either A (a score of 5-6), B (7-9), or C (10 or above). Decompensation indicates cirrhosis with a CP score of 7 or more (Class B).

^a Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

Child-Pugh criteria: (Pugh 1973, Lucey 1997, Vilstrup 2014).

7.4.4.1. Criteria for Assessing Cirrhosis

Acceptable methods of confirming (via medical history) or assessing cirrhosis include documented evidence or presence of one or more of the following cirrhosis indicators:

- Biopsy results consistent with PBC Stage 4 (Ludwig 1978)
- TE Median Value ≥ 16.9 kPa (Corpechot 2012)
- The presence of any of the following in the absence of acute liver failure:
 - Varices (including a history of esophageal varix ligation)
 - Ascites
 - Radiological evidence of cirrhosis (e.g., nodular liver or enlargement of portal vein and splenomegaly)
- Combined low platelet count ($<150,000/\mu\text{L}$) with:
 - persistent decrease in serum albumin, or
 - elevation in PT /INR (not due to antithrombotic agent use), or
 - elevated bilirubin (2x ULN)

7.4.4.2. Mayo Risk Score

Mayo Risk Score (MRS) ([Dickson 1989](#)) is calculated and reported within the EDC system based on data entered into the eCRF. Calculation of MRS includes Investigator assessment of peripheral edema and the use of diuretic therapy, which will be assessed during AE and concomitant medicine review at the scheduled visits and entered into the eCRF, as well as total bilirubin, albumin, and PT results obtained from the central laboratory data.

7.4.4.3. Potential Myopathy Evaluation and Monitoring

Subjects will be monitored for potential myopathy events throughout the study. If a subject becomes aware of the development of signs and symptoms of potential myopathy (i.e., muscle weakness, muscle soreness or muscle pain), the subject will be instructed to promptly contact the site for further assessment.

Clinical criteria for the monitoring of these events and the interruption/discontinuation of investigational product is as follows:

At screening: Check baseline creatine kinase (CK): If $\geq 5x$ ULN, then screen fail.

Previous History of Myalgia: Yes or No. If Yes, rate on a scale of 1 to 10 with 1 being the least amount of discomfort and 10 being the most amount of discomfort to establish baseline.

If subjects develop symptoms of myopathy at any point during the study, CK values must be checked. A CK $\geq 5x$ ULN or $\geq 3x$ ULN with symptoms consistent with rhabdomyolysis will require investigational product interruption. Laboratory values including CK and creatinine will be closely monitored until values return to baseline levels (see [Table 5](#)).

7.5. Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis

If a subject experiences symptoms suggestive of cholelithiasis and/or cholecystitis, the subject should undergo a complete evaluation consistent with the local standard of care, be assessed for appropriate treatment, including potential indication for surgery (e.g., cholecystectomy), and be monitored until resolution of clinical signs and symptoms. If symptomatic cholelithiasis and/or cholecystitis is diagnosed, investigational product should be permanently discontinued.

Investigational product should also be discontinued in the following instances:

1. Development of choledocholithiasis
2. Presence of any symptomatic gallbladder polyp; or
3. Presence of any gallbladder polyp >5 mm

7.6. Dosage Adjustment Criteria

7.6.1. DB Phase

The dosage for OCA (5 mg) should be maintained constant during the study. However, dose frequency may be modified for the management of pruritus or other safety findings as described in [Section 15.1.4.1](#).

In the event of tolerability issues such as pruritus or myalgia, the dosing frequency of all investigational product may be decreased at the discretion of the Investigator.

Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns.

Subjects who are discontinued from investigational product in the DB Phase should be scheduled for an early termination (ET) visit as close as possible to the last dose taken. Once the ET visit has been completed the subject should continue with their original scheduled visits until the end of the DB Phase where they would complete the ET visit and finish the study. These subjects will not participate in the LTSE portion of the study.

Refer to [Section 8.2.1](#) for guidance on mandatory discontinuation of investigational product due to severe and related AEs and progression to CP ≥ 7 (CP Class B or C).

Refer to [Section 8.2.2](#) for other reasons of discontinuation of investigational product (e.g., withdrawal of consent, lost to follow-up, or pregnancy).

7.6.2. LTSE Phase

Subjects who continue to meet protocol requirements will transition to the LTSE Phase (an open-label design) upon completion of the DB Phase. During the LTSE Phase, all subjects will be maintained (Treatment D subjects already on transition dose) or transitioned to OCA 5 mg + 400 mg BZF IR once daily.

Subjects who are transitioned to the OCA 5 mg + 400 mg BZF IR once daily dose (from BZF monotherapy or OCA 5 mg + 100 mg BZF IR) will be monitored with safety labs (liver biochemistries and CK levels) at 4 weeks after the transition, and if not significantly changed, then every 4 weeks until 12 weeks after the transition, at which point safety labs will be done every 3 months (unless there are significant changes in the labs which would be handled per protocol, refer to [Section 7.4](#)). Subjects who were on the OCA 5 mg + 400 mg BZF IR once daily dose during the DB-phase, will not warrant additional safety labs.

In the LTSE Phase, dose frequency may be modified for the management of pruritus or other safety findings as described in [Section 15.1.4.1](#). In the event of tolerability issues such as pruritus, the dosing frequency may be decreased at the discretion of the Investigator.

Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product in the LTSE Phase should schedule for the end of study (EOS) Visit and complete the study.

Refer to [Section 8.2.1](#) for guidance on mandatory discontinuation of investigational product due to severe and related AEs and progression to CP ≥ 7 (Class B or C). Refer to [Section 8.2.2](#) for other reasons of discontinuation of investigational product (e.g., withdrawal of consent, lost to follow-up, or pregnancy).

Subjects who were taking UDCA during the DB Phase of the study will continue this as a concomitant medication for the entirety of the LTSE Phase unless there is a tolerance or safety event related to UDCA that would require discontinuation.

7.7. Criteria for Study Termination

The Sponsor reserves the right to terminate the study at any time. In addition, the Sponsor may terminate the study at an investigational site at any time (e.g., Good Clinical Practice [GCP] noncompliance or poorly performing sites, as determined by the number of subjects enrolled or the quality of the study data).

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

Investigators will be informed by the Sponsor as to when the final study visit is to be completed and should then schedule all subjects for the EOS Visit.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 64 investigational study sites, globally with experience in treating subjects with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of subjects with PBC, from digital recruitment channels or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC subject societies, forums, or networks.

8.1.1. Subject Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with the EASL and the AASLD guidelines [[Lindor 2009a](#); [EASL 2017](#)]), as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:
 - History of elevated ALP levels for at least 6 months
 - Positive AMA titer, or if AMA negative or low titer ($\leq 1:80$), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (pyruvate dehydrogenase-E2, 2-oxo-glutaric acid dehydrogenase complex)
 - Liver biopsy results consistent with PBC (collected at any time before Screening)
2. At least one of the following qualifying biochemistry values (the mean of both Screening visits):
 - $ALP \geq 1.5 \times ULN$ but $\leq 1.67 \times ULN$ (will not exceed 25% of subjects enrolled in the study)
 - $ALP > 1.67 \times ULN$ (including up to 10% of subjects with $ALP > 5 \times ULN$)
 - Total bilirubin $> ULN$ but $< 2 \times ULN$
3. Age ≥ 18 years

4. Taking UDCA for at least 12 months (stable dose for ≥ 3 months) before Day 1 or no UDCA for 3 months before Day 1
5. Contraception: Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥ 1 highly effective method of contraception during the study and for 30 days after the end of treatment. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from exposure to investigational medicinal products.
 - Intrauterine device
 - intrauterine device (IUD)
 - intrauterine hormone-releasing system (IUS)
 - Bilateral tubal occlusion
 - Vasectomy (partner)
 - Combined (estrogen and progestogen containing) hormonal contraception (e.g., oral, intravaginal or transdermal) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
 - Progestogen-only hormonal contraception (e.g., oral, injectable or implantable) associated with inhibition of ovulation. If oral contraceptives are used, they must be used in combination with a male or female condom. Female subjects should have been on the hormone contraception for at least 8 days prior to Day 1.
 - Sexual abstinence, as a form of highly effective contraception, is defined as avoiding all types of sexual activity that could result in pregnancy during the entire period of the study treatment until at least 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study, including the LTSE Phase.
6. Must provide written informed consent and agree to comply with the study protocol.

8.1.2. Subject Exclusion Criteria

1. History or presence of other concomitant liver diseases including any of the following:
 - Hepatitis C virus (HCV) infection and ribonucleic acid positive
 - Active Hepatitis B virus (HBV) infection; however, subjects who have seroconverted [hepatitis B surface antigen negative (sAg-), hepatitis B surface antibody positive (sAb+); hepatitis B e-antigen negative (eAg-), hepatitis B e-antibody positive (eAb+); HBV DNA negative] may be included in this study after consultation with the Medical Monitor.
 - Subjects should be excluded if positive HBV DNA or HCV RNA

- Primary sclerosing cholangitis
 - Alcoholic liver disease
 - Definite autoimmune liver disease or PBC-AIH overlap
 - NASH
 - Gilbert's Syndrome (due to interpretability of bilirubin levels)
 - Rare liver conditions such as Wilson's disease, hemochromatosis, alpha-one anti-trypsin deficiency, or other conditions identified by the Investigator
2. Clinical complications of PBC including:
- History of liver transplant, current placement on a liver transplant list, or current MELD score >12. Subjects who are placed on a transplant list despite a relatively early disease stage (for example per regional guidelines) may be eligible as long as they do not meet any of the other exclusion criteria
3. History or presence of any of the following decompensating events:
- CP-Score ≥ 7
 - Clinical evidence of decompensated liver disease or portal hypertension
 - Varices (including a history of esophageal varix ligation)
 - Ascites/hepatic hydrothorax
 - Spontaneous bacterial peritonitis
 - Hepatic encephalopathy
 - Jaundice (with total bilirubin >3 mg/dL [$>51.3 \mu\text{mol/L}$])
 - Biochemical evidence of hepatic impairment, hepatic decompensation, or injury in at least one of the following:
 - Total bilirubin >3 mg/dL ($>51.3 \mu\text{mol/L}$)
 - INR >1.7
 - Albumin <3.5 g/dL
 - MELD >12
 - ALT >5X ULN
 - Known or suspected hepatocellular carcinoma (HCC)
 - Prior trans-jugular intrahepatic portosystemic or peritoneovenous shunt procedure
 - Hepatorenal syndrome (type I or II) or serum creatinine >1.5 mg/dL ($135 \mu\text{mol/L}$) at Screening Visits 1 and 2
 - Portopulmonary hypertension
 - Hepatopulmonary syndrome

4. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) or which may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign conditions)
5. Presence of any other disease or condition that interferes with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the intestine (e.g., inflammatory bowel disease or gastric bypass procedure [gastric lap band is acceptable])
6. History of or current gallbladder diseases:
 - Cholelithiasis or cholecystitis without prior cholecystectomy
 - Choledocholithiasis without documented complete stone removal (e.g., via ERCP) and cholecystectomy
 - Any size symptomatic gallbladder polyp
 - Gallbladder polyp >5 mm
7. History or current pancreatitis
8. History of drug-induced myopathy
9. Chronic kidney disease (CKD) (serum creatinine >1.5 mg/dL [$>135 \mu\text{mol/L}$]; creatinine clearance <60 mL/min) or undergoing dialysis
10. Platelet count <150,000/ μL at Screening Visits 1 and 2 (an average of both Screening visits)
11. Known history of human immunodeficiency virus (HIV) infection
12. History or presence of clinically concerning cardiac arrhythmias likely to affect survival during the study, or Screening (pretreatment) QT or QTc interval of >450 milliseconds for males and >470 milliseconds for females
13. Severe pruritus, as defined in [Table 15](#), or required systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin) within 2 months of Day 1. Subjects who plan to use or will use BAS during the study will not be eligible.
14. History of known or suspected clinically significant (CS) hypersensitivity to OCA, BZF, or other fibrates or any of their components
15. Known photoallergic or phototoxic reactions to fibrates
16. If female, known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
17. Other CS medical conditions that are not well controlled or for which medication needs are anticipated to change during the study (e.g., Type 2 diabetes mellitus, hypothyroidism, nephritic syndrome, dysproteinemia, obstructive liver disease, dyslipidemia) and/or up to the discretion of the Principal Investigator
18. Treatment with the following medications 30 days before Day 1 or plans to use these medications during the study: azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, statins, budesonide and other systemic corticosteroids, monoamine oxidase inhibitors (MAOIs), and potentially hepatotoxic drugs (including α -methyl-dopa, sodium valproic acid, isoniazide, and nitrofurantoin)

19. Treatment with the following medications 12 months before Day 1 or plans to use these medications during the study: antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
20. Participation in a study of another investigational medicine, or device within 30 days before Screening
21. Treatment with commercially available OCA or participation in a previous study involving OCA or other FXR agonists, or PPAR-agonists within 3 months before Screening
22. Unable to tolerate BZF or other fibrates, treatment with commercially available fibrates, or participation in a previous study involving fibrates within 3 months before Screening
23. History of or ongoing alcohol or drug abuse within 1 year before Day 1. Subjects with moderate alcohol use within the past 3 months will be excluded from this study. Moderate alcohol consumption is defined as 1 standard drink per day for women and 2 drinks per day for men; whereby 1 standard drink is equivalent to: 12 oz beer (5% alcohol); 5 ounces of wine (12% alcohol), and 1.5 ounces of 80 proof (40% alcohol)
24. History of noncompliance with medical regimens, or is considered by the investigator not able to meet the requirements as specified in the protocol at the Screening visits and throughout the duration of the study
25. Blood or plasma donation within 30 days before Day 1
26. Mental instability of incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
27. A CK value at Screening $\geq 5 \times$ ULN or any abnormal laboratory value that is considered CS in the opinion of the Investigator and Sponsor (at either Screening visit)
28. Known or suspected nephrotic syndrome based on the following diagnostic criteria (both Type 1 and Type 2):
 - Proteinuria, spot urine protein: albumin/creatinine ratio (ACR) of >300 mg/mmol (subjects with normal renal function and ACR values analyzed to be below the lower limits of detection are permitted)
 - Serum albumin <25 g/L
 - Clinical evidence of peripheral edema
 - Severe hyperlipidemia (total cholesterol above >10 mmol/L)

For US sites where HepQuant SHUNT will be conducted, the following exclusion criteria will only apply for subjects who are participating in the HepQuant SHUNT procedure:

1. Subjects with a history of known or suspected hypersensitivity to any ingredient in human albumin preparations
2. Subjects with uncontrolled hypertension (defined as a diastolic blood pressure of 110 mmHg or higher)
3. Subjects with extensive resection of large segments of small intestine (short gut) or severe gastroparesis

4. Subjects on either a non-selective beta blocker or an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) who are unwilling to delay taking their normal dose the morning of their testing

8.2. Subject Withdrawal Criteria

Subjects who are discontinued from investigational product are expected to continue in the study during the DB Phase and should follow the regular visit schedule or at least until the concern is resolved or stabilized.

Subjects who are discontinued from investigational product during the DB Phase will be scheduled for an ET visit, refer to [Section 9.7.6](#).

Subjects who are discontinued from investigational product during the LTSE Phase will be scheduled for an EOS Visit.

8.2.1. Reasons for Mandatory Discontinuation of Investigational Product

Subjects will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for monitoring these events are summarized in [Table 6](#).

Investigational product will be discontinued permanently if the subject received a liver transplant or experiences other potential hepatic decompensation events as defined in Table 6. Subjects should be closely monitored until normalization or stabilization and should continue to return for scheduled study visits for safety follow up.

8.2.1.1. Severe and Related Adverse Events

If a subject experiences an AE that is $\geq$ Grade 3 in severity using criteria outlined in [Section 15.1.4](#) and is considered possibly, probably, or definitely related to the investigational product, the investigational product must be discontinued. However, subjects should be encouraged to continue study visits, despite stopping investigational product, for continued collection of safety data but may withdraw consent at any time. If investigational product is stopped, visits would continue only until the end of study in the DB Phase; the subject should not be allowed to enter the LTSE Phase.

8.2.1.2. Pregnancy

If a female subject becomes pregnant, she must discontinue treatment with investigational product immediately during the DB Phase and undergo an ET visit. If a female should become pregnant during the LTSE Phase, she must discontinue treatment with investigational product immediately and undergo an EOS. As described in [Section 15.1.9](#), pregnancy is not considered an AE for reporting purposes.

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

Subjects who discontinue investigational product will be requested to continue in the study through the DB Phase; however, subjects are free to discontinue at any time. Subjects who discontinue investigational product before completing the DB Phase need to also continue to follow the regular visit schedule through to DB Week 12 visit. ET procedures should only be

conducted if the subject withdraws consent during the DB Phase or discontinues treatment (see [Section 9.7.6](#)).

Subjects who discontinue investigational product during the LTSE Phase will need to undergo the EOS Visit. Subjects will not be required to have scheduled visits between discontinuation of investigational product and EOS visit.

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

- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject
- Withdrawal of consent:
 - Consent may be fully withdrawn
- Lost to follow-up
- Pregnancy
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important
- There is a major violation of the clinical study protocol
- The development of any medical conditions listed in the exclusion criteria that might jeopardize subject safety ([Section 8.1.2](#))

The Investigator is encouraged to contact the Sponsor before discontinuing a subject from treatment. The Investigator must notify the Sponsor study monitor, also known as the Clinical Research Associate (CRA), by telephone or email as soon as possible if any subject prematurely withdraws from the study.

The Sponsor may terminate this study at any time.

8.2.2.1. Withdrawal of Consent to Continue in the Study

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

A reasonable effort must be made to determine the reason(s) for subject discontinuation. This information and date of contact must be recorded on the eCRF.

8.2.2.2. Lost to Follow-Up

If a subject fails to complete a study visit, and the Investigator ceases to have contact with the subject, he or she will be withdrawn from the study. Subjects will be considered “lost to follow-up” only after reasonable, documented attempts to reach the subject prove unsuccessful.

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject fails to complete a study visit or is lost to follow-up. This information and date of contact must be recorded on the eCRF.

8.2.3. Subject Discontinuation Notification

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

DB Phase: If a subject is withdrawn from the study early (regardless of the cause), all of the ET treatment evaluations are to be performed at the time of withdrawal, to the extent possible.

LTSE Phase: If a subject is withdrawn from the study early (regardless of the cause), all of the EOS evaluations are to be performed at the time of withdrawal, to the extent possible.

8.2.4. Subject Withdrawal from the HepQuant SHUNT Procedure

Subject Discontinuation

In the event of an allergic or anaphylactic reaction to albumin, Investigators must suspend administration of the cholates and manage the subject according to standard of care. Any subject with a hypersensitivity reaction to any component of the HepQuant SHUNT Kit will be withdrawn and will not undergo any further HepQuant procedure. Any subject who experiences an unanticipated SAE that is determined to be related to the HepQuant test or any component of the HepQuant SHUNT test kit will not undergo further testing with the HepQuant SHUNT Kit. Subjects that are withdrawn from the HepQuant-SHUNT procedure are expected to continue in the main study.

Discontinuation of Use of the HepQuant-SHUNT Kit

Use of the HepQuant-SHUNT Kit in this study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for suspension or termination, will be provided by the suspending or terminating party to the study participants, Investigators, Investigational Device Exemption Sponsor, and regulatory authorities. If use of the kit is prematurely terminated or suspended, the Investigator will promptly inform study participants, the IRB, and the Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of any resulting changes to study visit schedule.

The HepQuant portion of the study will be entirely stopped if two or more events meeting the definition of an Unanticipated Adverse Device Effect 21 CFR (812.3(s)) occur. Complete details regarding the HepQuant SHUNT test and its use in this study may be found in [Appendix B](#).

9. TREATMENT OF SUBJECTS

9.1. Investigational Products Treatment Regimen

The term “investigational products” (provided as part of this clinical study) refers to the following:

- OCA Placebo tablet
- OCA 5 mg tablet

- BZF Placebo tablet
- BZF 100 mg IR tablet
- BZF 200 mg IR tablet

Investigational products will be taken orally once daily for the duration of the study. Subjects will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time each day (including UDCA) with food and water (ad libitum).

Subjects will be assigned to either AM or PM dosing, according to [Section 9.4.1](#). Subjects assigned to AM dosing will be instructed to begin dosing on Day 1 and to take investigational product between 7 AM-11 AM at approximately the same time each day. Subjects assigned to PM dosing will be instructed to take investigational product between 2 PM-5 PM for the entire DB Phase.

After completion of the DB Phase, all subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits). Subjects must be instructed to swallow the tablets whole; investigational product must not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout study conduct.

9.1.1. Dosing Instructions at Site

9.1.1.1. AM Dosing

At each study visit the daily dose of investigational product should be administered at the site for subjects who dose investigational product in the AM. All assessments must be completed before administration of investigational product and UDCA (if applicable), except for the serial PK samples. A low-fat meal or meal replacement drink will be given with investigational product administration at the Week 4 study visit. The low-fat meal or meal replacement drink will be provided by the site personnel.

9.1.1.2. PM Dosing

For subjects who dose investigational product in the PM, investigational product will not be administered at the study visit. Subjects will receive a low-fat meal or meal replacement drink in the morning at the Week 4 visit prior to PK sampling.

9.2. Concomitant Medications

Subjects must follow the medication restrictions outlined in the inclusion and exclusion criteria ([Section 8](#)) during the study.

Relevant information about all concomitant medications (including prescribed, over the counter, or herbal preparations) taken before (i.e., within 30 days of Day 1) and during the study must be recorded in the source documents and eCRF, as well as any dose or dose regimen changes that occur during the study. [REDACTED]

9.2.1. Statins

Use of statins (e.g., simvastatin, atorvastatin) is not allowed during the study.

9.2.2. Monoamine Oxidase Inhibitors

Use of MAOIs (e.g., isocarboxazid, phenelzine, selegiline, and tranylcypromine) is not allowed during the study.

9.2.3. Anticoagulants

Use of anticoagulants (e.g., warfarin) should be monitored and the dose adjusted, if needed. Taken concomitantly, OCA and warfarin may decrease INR, and BZF may potentiate the action of coumadin-type anticoagulants.

9.2.4. Antidiabetics

BZF may potentiate the action of antidiabetic medications (including insulin) requiring increased monitoring of glycemic status.

9.2.5. Bile Acid Sequestrants

Use of BAS (including cholestyramine and its derivatives, colestipol, colesevelam, or other BAS) or aluminum hydroxide- or smectite-containing antacids is not allowed during the trial since it may alter the interpretation of the effects of BZF on pruritus.

9.2.6. Estrogens

Because estrogens may lead to a rise in lipid levels, the use of BZF in subjects taking estrogens or estrogen-containing contraceptives during the study must be critically considered on an individual basis and is up to the Principal Investigator's discretion.

9.2.7. Drug-Drug Interaction**OCA**

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. OCA 10 mg and 25 mg increased sensitive CYP1A2 probe, caffeine, exposure 42% and 65%, respectively, suggesting weak inhibition of CYP1A2 in this dose range. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

Although OCA did not affect systemic exposure to sensitive CYP2C9 probes like warfarin a slight decrease in International Normalized Ratio was observed with OCA suggesting a possible pharmacodynamic interaction altering warfarin efficacy.

BZF

For BZF, caution should be exercised when oral anticoagulants are given with BZF SR. The dosage of anticoagulants should be reduced up to 50% to maintain the PT at the desired level to prevent bleeding complications. Careful, frequent (perhaps weekly) monitoring of PT is therefore recommended until it has been determined that prothrombin levels are stabilized. Assessment and dosing regimen of anticoagulants is left up to the Principal Investigator's discretion.

HMG CoA reductase inhibitors: Interaction between fibrates and HMG CoA reductase inhibitors (statins) may vary in nature and intensity depending on the combination of the administered drugs. Due to the risk of rhabdomyolysis, BZF should only be administered together with HMG CoA reductase inhibitors in exceptional cases when strictly indicated. Subjects receiving this combination therapy must be fully educated or fully informed carefully of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the first signs of myopathy. This combination therapy must not be used in subjects with predisposing factors for myopathy (impaired renal function, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance, and a high alcohol intake).

Cyclosporine: Severe myositis and rhabdomyolysis have occurred when a cyclosporine was administered with a fibrate. Therefore, the benefits and risks of using BZF SR concomitantly with cyclosporine should be carefully considered and is up to the Principal Investigator's discretion.

Immuno-suppressant therapies: In isolated cases, reversible impairment of renal function (accompanied by a corresponding increase in the serum creatinine level) has been reported in organ transplant subjects receiving immuno-suppressant therapy and concomitant BZF. Renal function should be closely monitored in these subjects and in the event of relevant significant changes in laboratory parameters, BZF should be discontinued.

Insulin and sulfonylureas: serious hypoglycemia may result in the combinatory use of BZF and hypoglycemic agents.

MAOIs: MAOIs (with hepatotoxic potential) must not be administered together with BZF SR.

Resins: Cholestyramine or any other resin should not be administered together with BZF since the absorption of BZF is impaired by cholestyramine.

Estrogens: Since estrogens may lead to a rise in lipid levels, the prescribing of BZF SR in subjects taking estrogens or estrogen-containing contraceptives must be critically considered on an individual basis.

Rosiglitazone: Some epidemiologic studies and case reports suggest that markedly decreased high density lipoprotein cholesterol in some subjects involves the interaction of rosiglitazone with fenofibrate or BZF.

9.3. Treatment Compliance

The Investigator should assess the subject's compliance with dosing of investigational product at each study visit and phone call after Day 1.

Subjects should be instructed to retain all bottles and blister packs of investigational product, even if empty, and to provide them to the Investigator at the indicated visits in [Table 3](#) and [Table 4](#). The Investigator or designee should perform investigational product accountability (i.e., count of returned tablets) and, if applicable, follow up with the subject to retrieve any investigational product bottles or blister packs that have not been returned.

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

9.4. Randomization and Blinding

9.4.1. Methods of Assigning Subjects to Treatment Groups

This study will be conducted in a double-blind (subjects and site staff), randomized manner. Enrolled subjects will be randomized in a 1:1:1:1 ratio to one of the following treatment groups:

<u>Treatment A:</u> BZF 100 mg IR tablet once daily	OCA placebo tablet BZF 100 mg IR tablet BZF placebo tablet
<u>Treatment B:</u> BZF 400 mg IR tablet once daily	OCA placebo tablet BZF 200 mg IR tablet BZF 200 mg IR tablet
<u>Treatment C:</u> OCA 5 mg once daily + BZF 100 mg IR once daily	OCA 5 mg tablet BZF 100 mg IR tablet BZF placebo tablet
<u>Treatment D:</u> OCA 5 mg once daily + BZF 400 mg IR once daily	OCA 5 mg tablet BZF 200 mg IR tablet BZF 200 mg IR tablet

All subjects will be assigned investigational product according to their treatment group from Day 1 using an interactive web response system (IWRS).

Randomization will be stratified at baseline by the following:

- Total bilirubin levels ($\leq 0.7x$ or $> 0.7x$ upper limit of normal [ULN] but $< 2x$ ULN)
- ALP ($\geq 1.5x$ ULN but $\leq 1.67x$ ULN or $> 1.67x$ ULN)

Note: The number of subjects with baseline ALP $\geq 1.5x$ ULN but $\leq 1.67x$ ULN will not exceed 25% of subjects enrolled in the study and will include up to 10% of subjects with ALP $> 5x$ ULN.

The IWRS will serve as the investigational product inventory and management system and may be integrated with the study database.

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

To maintain blinding throughout the DB Phase, all investigational product dispensed for all treatment arms will be identical in appearance.

Once a subject is scheduled to be enrolled, the clinical site will inform the unblinded statistician via secured and restricted email (unblindedstats@interceptpharma.com) at least 3 to 4 days prior to dosing. The unblinded statistician will allocate the first 3 subjects in each treatment arm to PM dosing. The IRT system will notify the unblinded statistician by an auto-generated alert after the first 3 subjects in one treatment arm are randomized. All subsequent subjects in the same treatment arm will be allocated to AM dosing. The unblinded statistician responsible for randomization will not be involved in the regular study operations and will have no communication with study team members or be involved in the interim analyses.

9.4.2. Blinding

All subjects and operational site staff will remain blinded until the database is locked for the DB Phase.

The Sponsor will use data output from interim analyses from the DB phase for purposes of regulatory interactions and subsequent Phase 3 trial design planning. The SAP will specify the methods for the interim analyses, as well as additional details on the conduct (see [Section 16.7](#)).

Rolling Interim Analysis

The Sponsor will perform an unblinded rolling analysis of efficacy, PK, and safety data throughout the DB phase. Details of the unblinding and Data Access Plan, including Sponsor Staff that will be unblinded, will be provided in separate documents.

DMC Interim Safety Analysis

The Data Monitoring Committee (DMC) will perform an interim safety analysis when approximately 32 subjects complete the Week 12 visit in accordance with the DMC Charter. The DMC will review the interim criterion for safety data and other relevant information to determine whether to recommend and continue the study.

9.4.3. Emergency Unblinding Procedures

Treatment assignments for individual subjects will be made available to the Investigator and the Contract Research Organization Medical Monitor for medical emergency use only through the IWRS system. When possible, the Medical Monitor should be consulted if a medical emergency necessitates unblinding (i.e., in situations where knowledge of the blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as accidental unblinding or unblinding due to a SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual subject for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study correspondence the rationale, circumstances, and the person or persons being informed about the unblinding.

Access to randomization codes and corresponding treatment assignments will also be made available through the IWRS system to the designated Intercept staff responsible for unblinding suspected unexpected serious adverse reactions (SUSARs) for reporting to the Regulatory Authorities.

9.5. Assignment of Site and Subject Numbers

9.5.1. Site Numbers

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

9.5.2. Subject Numbers

Subjects will be assigned a unique 10-character identifier (AAA-BBBCCC), independent of the randomization number. The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits represent the site number (BBB). The last 3 digits represent a unique screening number that is assigned in sequential order at each site starting with 001 (CCC).

9.6. Restrictions

All subjects must fast for at least 8 hours before Screening Visit 2 and all subsequent study visits. All analytes will be assayed in fasting serum or plasma samples ([Table 3](#) and [Table 4](#)). Water is permitted during the fasting period.

9.7. Visit Procedures

The visit procedures are provided in Table 3 and Table 4. Additional information is provided in the following sections.

9.7.1. Informed Consent Procedures

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

9.7.2. Screening Visit Procedures

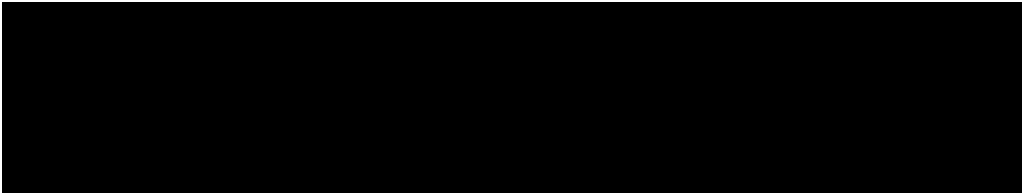
Subjects will be screened for a period of 2 weeks to a maximum of 8 weeks before entering the study to allow for the collection of repeat serum chemistry samples (at least 2 weeks apart) for verification of inclusion/exclusion criteria and establishing baseline. Rescreening will be allowed at the discretion of the Sponsor.

Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. Visit windows are listed in Table 3.

9.7.2.1. Screening Visit 1

Screening Visit 1 procedures for all subjects are as follows:

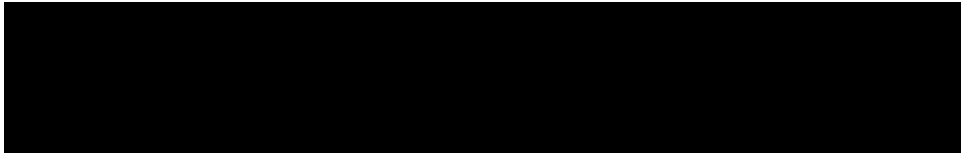
- Review ICF and obtain signatures before performing any study-related procedures, including Screening procedures
- Collect medical/surgical history including history of myalgia (refer to [Section 7.4.4.3](#) for additional instructions) and PBC history/demographics
- Assess and record any pretreatment AEs including myopathy evaluation (after the ICF has been signed)

- Record prior (if taken within 30 days of Day 1) and current concomitant medications
- Verify inclusion and exclusion criteria for eligibility
- Conduct a physical examination
- Measure height and record weight and body mass index (BMI) and waist-to-hip ratio (WHR)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Perform standard 12-lead electrocardiogram (ECG)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - 
 - MRS
 - CP Score/Class (assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring.)
- 
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, and total and conjugated bilirubin and lipid panel (laboratory values may be repeated within 8 weeks). The most recent laboratory value should be used to confirm Screening requirements.
 - Virology: HCV/hBsAg. Autoimmune hepatitis (e.g., antinuclear antibody, anti-smooth muscle antibody, anti-actin antibodies).
 - Thyroid hormones: free T3, free T4, and TSH
- Urinalysis
- Perform a urine-based beta human chorionic gonadotropin (β -hCG) pregnancy test for females of childbearing potential. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory. A female of childbearing potential is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Ultrasound exam of the right upper quadrant (of the abdomen) for cholelithiasis and gallbladder disease. Record subjects' common bile duct diameter.

- Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted). Fasting is required before Screening Visit 2.

9.7.2.2. Screening Visit 2

Screening Visit 2 procedures for all subjects are as follows:

- Verify that the subject has fasted for at least 8 hours
- Update medical/surgical history including history of myalgia (refer to [Section 7.4.4.3](#) for additional instructions) and PBC history/demographics
- Assess and record any pretreatment AEs including myopathy evaluation
- Record prior and current concomitant medications
- Verify inclusion and exclusion criteria for eligibility
- Record weight, BMI and WHR
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - 
 - MRS
 - CP Score/Class (assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring.)
 - 
 - 
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, and total and conjugated bilirubin and lipid panel (laboratory values may be repeated within 8 weeks)
- Urinalysis
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted)

9.7.3. Day -4 to -3

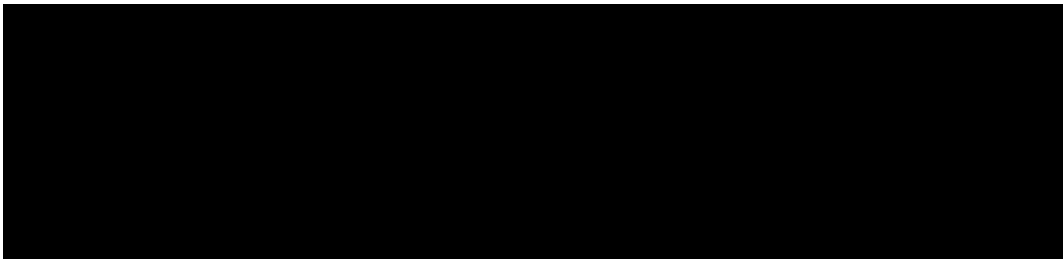
- Once a subject is scheduled to be enrolled, the clinical site will inform the unblinded statistician via secured and restricted email (unblindedstats@interceptpharma.com). The unblinded statistician will send an email to the site to provide dosing time (i.e., AM or PM) for the subject.

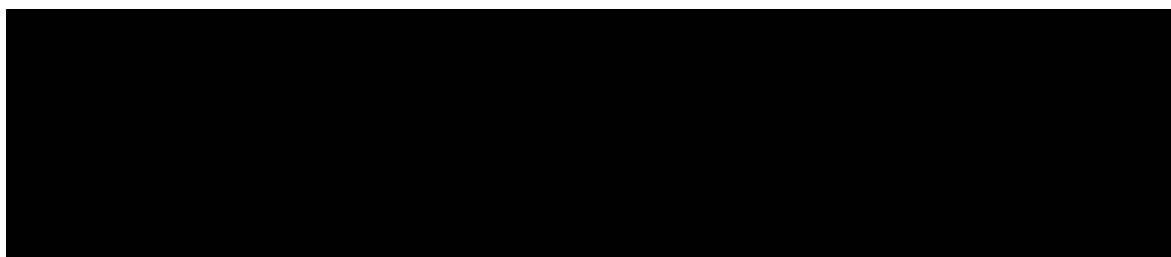
The unblinded statistician responsible for randomization will not be involved in the regular study operations and will have no communication with study team members or be involved in the interim analyses.

9.7.4. Day 1 Procedures

All Day 1 procedures should be performed prior to dosing (the maximum time from Screening Visit 1 to Day 1 should be 8 weeks). Day 1 Visit procedures for all subjects are as follows:

- Access to IWRS for subject randomization/treatment assignment
- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having eaten or drunk within 8 hours, other than water, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits. Refer to [Section 14.1](#) for additional instructions.
- Assess pre-treatment AEs
- Monitor for potential myopathy
- Record prior and current concomitant medications
- Collect medical history and PBC history/demographics to include assessment of pruritus at baseline only
- Verify inclusion and exclusion criteria for eligibility
- Conduct a physical examination
- Record weight, BMI and WHR
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - [REDACTED]
 - MRS
 - CP Score/Class (assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring.)
 - [REDACTED]
 - [REDACTED]
- [REDACTED]
- [REDACTED]

- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - 
 -
 -
 -
- Urinalysis
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory. No investigational product should be administered if a urine pregnancy test is positive.



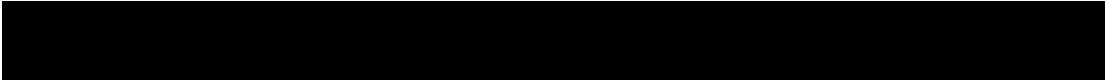
- Dispense/administer investigational product (during clinic visit). Subjects should be instructed to either take investigational product in the morning (AM dosing) or afternoon/evening (PM dosing) per IWRS dosing assignment.
- Remind subject to fast ≥ 8 hours prior to Weeks 2, 4, 6, 8, 10, and 12

9.7.5. Week 2, 4, 6, 8, 10, and Week 12/LTSE Day 1

The following procedures will be performed at Weeks 2, 4, 6, 8, 10, and 12 (LTSE Day 1), with exceptions noted:

- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Assess AEs
- Conduct a physical examination (Week 12 only)
- Monitor for potential myopathy
- Record prior and current concomitant medications

- Record weight, BMI and WHR (also record height for Week 12)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - [REDACTED]
 - MRS
 - CP Score/Class (assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring.)
 - [REDACTED]
 - [REDACTED]
- TE (Weeks 8, 10 and 12 only) (at qualifying sites only)
- [REDACTED]
- Perform standard 12-lead ECG (Week 12 only)
- [REDACTED]
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. Include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - Thyroid hormones: free T3, free T4, and TSH (Week 12 only)
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Urinalysis
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential

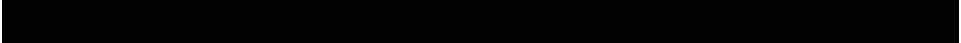
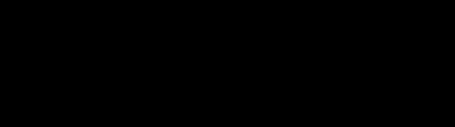
- 
- Dispense/administer investigational product (Weeks 4, 8, and 12 only).
 - Remind subject to maintain either AM or PM dosing (Weeks 2, 4, 6, 8, 10, and 12).
 - Remind subject to fast ≥ 8 hours prior to next dosing visit
 - Assess investigational product accountability and compliance

9.7.6. Early Termination Procedures for Subjects who Withdraw from Investigational Product or Withdraw Consent During the DB Phase

Subjects who discontinue investigational product are expected to continue attending regularly scheduled study visits until the end of the DB Phase (Week 12) or at the discretion of the Sponsor.

Early terminations procedures, required whenever subjects discontinue treatment with investigational product in the DB Phase, will be performed at the ET visit. The ET visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. The actual investigational product discontinuation scenario ([Table 8](#)) will determine the sequence of the ET visit and procedures.

The following procedures will be performed at the ET visit:

- Assess AEs
- Monitor for potential myopathy
- Record prior and current concomitant medications
- Physical examination
- Record weight and BMI and WHR
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 -  .
 - MRS
 - CP Score/Class (assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring.)
 - 
 - 

- [REDACTED]
- [REDACTED]
- Perform standard 12-lead ECG
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - Thyroid hormones: free T3, free T4, and TSH
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Assess investigational product accountability and compliance
- Urinalysis
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential

When a subject ends participation in the study (e.g., at a point between standard study visits) either due to withdrawal of consent or investigational product discontinuation, an ET visit must be performed as near as possible to the last dose of investigational product, and the procedures must be performed as listed in Table 8. The purpose of this visit is to conduct complete and/or final assessments on or as near as possible to the final day of dosing. In some cases, the subject may discontinue on the day of a scheduled study visit. In these cases, ET visit procedures should be performed in place of the scheduled study visit procedures. The data will be recorded as ET procedures in the eCRF.

Table 8: Early Discontinuation Scenarios for the Double-Blind Phase

	Investigational Product (IP)	Consent	Study Visit Status	ET Visit ^a
Early Termination	Discontinued	Withdrawn	No additional visits except ET visit	Combined visit, completed as close as possible to last dose of IP
Treatment Discontinuation	Discontinued	Active	Regular visit schedule	Complete as close as possible to last dose of IP
Sponsor Termination	Discontinued	NA	No additional visits except ET visit	Combined visit, completed as close as possible to last dose of IP
Lost to Follow-Up	Discontinued	LTF	None	Unable to complete due to LTF status

DB = double-blind; ET = early termination; IP = investigational product; LTF = lost to follow-up; NA = not applicable

^a Refer to Table 3 for all procedures and evaluations required at the ET visit.

9.7.7. **Unscheduled/Safety Visit**

The Investigator may schedule an Unscheduled/Safety Visit at any time if clinically warranted based on Investigator discretion. A PK sample should be collected if an unscheduled visit occurs due to a safety event. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted as shown in [Table 4](#). As appropriate, the Medical Monitor should be contacted.

9.7.8. **LTSE Phase**

Upon completion of the DB Phase, subjects who continue to meet protocol requirements will transition to the LTSE Phase and continue or transition onto the Treatment D dose. All subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits). The end of the trial is determined to be last subject last visit (LPLV) in the LTSE Phase.

9.7.8.1. **LTSE Day 1 (Week 12 DB Phase)**

LTSE Day 1 will be the last visit (Week 12) in the DB Phase. Procedures performed at this visit are listed in [Section 9.7.5](#).

9.7.8.2. **Week 16**

The following procedures will be performed:

- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Record concomitant medications
- Assess AEs
- Monitor for potential myopathy
- Record weight, BMI and WHR
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - [REDACTED]
 - MRS
 - CP Score/Class (assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring)
 - [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- Assess investigational product accountability and compliance
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - Thyroid Hormones: Free T3, free T4, and TSH
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- Urinalysis
- [REDACTED] No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.
- Dispense/administer investigational product
- Remind subject to fast ≥ 8 hours prior to next dosing visit

9.7.8.3. Week 20 (Telephone Visit and Laboratory Evaluations)

LTSE Week 8 will be conducted by telephone call outside of the laboratory evaluations being collected. Subjects will be contacted for the following:

The following procedures will be performed:

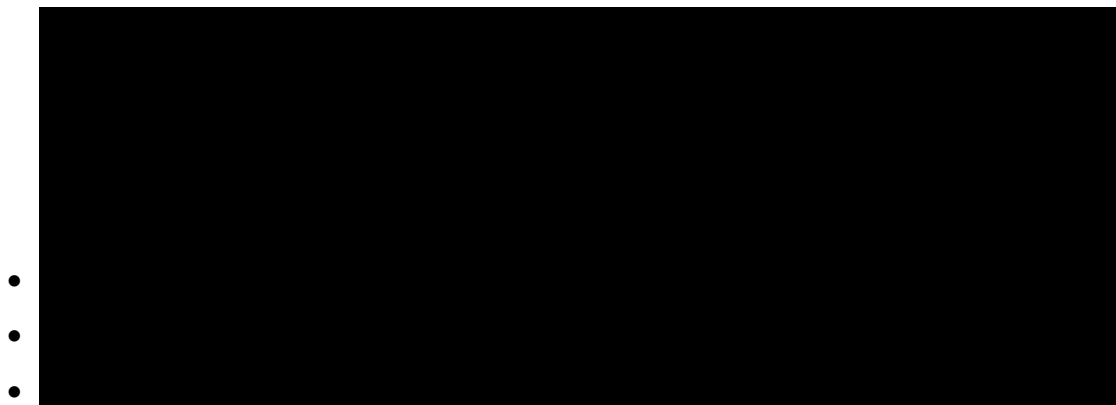
- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- Urinalysis
- MRS
- [REDACTED] No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.

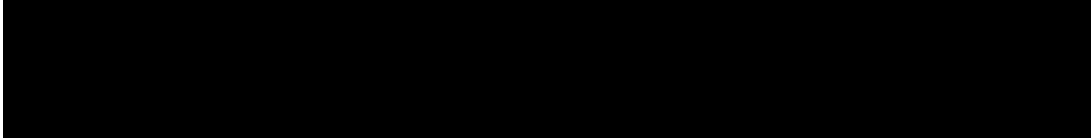
- Assess investigational product accountability and compliance
- Record concomitant medications
- Assess AEs
- Monitor for potential myopathy
- Remind subject to fast ≥ 8 hours prior to next dosing visit

9.7.8.4. Week 24

The following procedures will be performed:

- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Assess AEs
- Monitor for potential myopathy
- Record concomitant medications
- Record weight, BMI and WHR
- Conduct a physical examination
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - 
 - MRS



- 
- Assess investigational product accountability and compliance
- Obtain blood samples for the following:

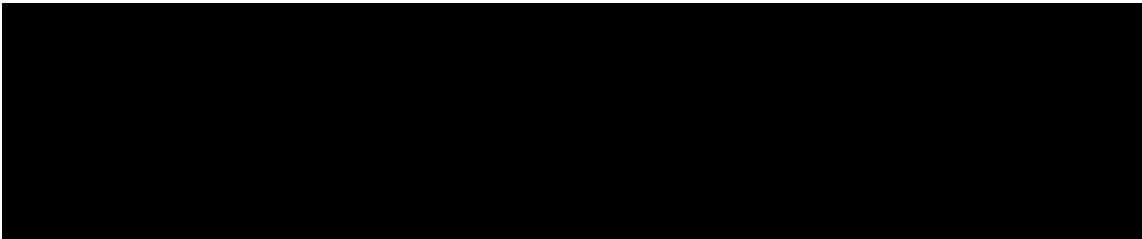
- Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
- [REDACTED]
- [REDACTED]
- Urinalysis
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- TE (at qualifying sites only)
- [REDACTED]. No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.
- Dispense/administer investigational product
- Remind subject to fast ≥ 8 hours prior to next dosing visit

9.7.8.5. Weeks 36, 60, 84, 108, and 132

The following procedures will be performed:

- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Record concomitant medications
- Assess AEs
- Monitor for potential myopathy
- Record weight, BMI and WHR
- Perform physical examination
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - [REDACTED]
 - MRS
 - CP Score/Class (Assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring)
 - [REDACTED]

-
-
-

- Assess investigational product accountability and compliance
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - Thyroid Hormones: Free T3, free T4, and TSH
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- 
No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.
- Urinalysis
- Dispense/administer investigational product
- Remind subject to fast ≥ 8 hours prior to next dosing visit
- 

9.7.8.6. Weeks 48, 72, 96, 120, and 144

The following procedures will be performed:

- Verify that the subject has fasted for at least 8 hours
 - Record fasting status in the source and eCRF
 - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Record concomitant medications
- Assess AEs
- Monitor for potential myopathy
- Record weight, BMI and WHR
- Perform physical examination

- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - [REDACTED]
 - MRS
 - CP Score/Class (Assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring)
 - [REDACTED]
 - [REDACTED]
- TE (at qualifying sites only)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Assess investigational product accountability and compliance
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - [REDACTED]
 - [REDACTED]
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- [REDACTED]. No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.
- Urinalysis
- Dispense/administer investigational product
- Remind subject to fast ≥ 8 hours prior to next dosing visit

9.7.8.7. LTSE Week 156 (EOS Visit)

The following procedures will be performed at the LTSE Week 156/EOS Visit:

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

- If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF
- Assess AEs
- Monitor for potential myopathy
- Record concomitant medications
- Record weight, BMI and WHR
- Conduct a physical examination
- Perform standard 12-lead ECG
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Calculations will be performed by the Sponsor or designee for the following and recorded on the eCRF:
 - [REDACTED]
 - MRS
 - CP Score/Class (Assessment of ascites and hepatic encephalopathy is required. See [Section 7.4.4](#) for additional information regarding CP scoring.)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- Assess investigational product accountability and compliance
- Obtain blood samples for the following:
 - Serum chemistry, hematology, and coagulation. To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, total and conjugated bilirubin, and lipid panel
 - Thyroid Hormones (Free T3, free T4, and TSH)
- Urinalysis
- Perform a urine-based β -hCG pregnancy test for females of childbearing potential
- [REDACTED]. No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.

10. STUDY MANAGEMENT DURING COVID-19

The COVID-19 infection control measures that have been imposed by local and national governments to contain the COVID-19 pandemic have resulted in some study sites not being able to perform protocol-specified procedures and assessments such as collecting laboratory samples. In addition, some subjects are unable to return to study sites for evaluations and/or to receive continued supply of investigational product. Enforcement of many restrictions by local authorities have also affected the site monitor's ability to perform on-site monitoring during the pandemic.

This section describes the processes under which subjects who are unable or unwilling to return to study sites may complete protocol-specified assessments and continue to receive investigational product until in-person site visits can resume. To ensure the continued safety monitoring of the participating subject and to minimize the potential adverse impact on achieving the objectives of the study due to the restrictions from the COVID-19 pandemic, the following approaches may be applied to the study protocol. Investigators should document the reason for any contingency measures implemented and how restrictions related to COVID-19 led to the changes in study conduct, duration of those changes, and how those study participants were impacted.

10.1. Alternative Approaches for Study Conduct Due to COVID-19

For subjects who are unable to attend in-person study visits due to national or local restrictions, the following alternative options are deemed acceptable, upon required Ethic Committee or Regulatory Agency approval, to satisfy the requirements for continued supply of investigational product:

- **Subject Consent:** If re-consent is necessary alternative ways of obtaining re-consent should be considered, including obtaining oral consent via phone or video-call supplemented with e-mail confirmation. If the technology is available, then electronic methods of obtaining informed consent such as DocuSign® would also be considered.
- **Subject Assessment:** In place of in-person visits, assessment of subjects may be performed using a “virtual visit” including phone consultation, or video (telemedicine) visits by authorized investigators to undertake examinations on the study. All assessments should adhere as closely as possible to the visit windows specified in the protocol schedule of visits. In case this is not possible, please discuss with the Medical Monitor or Sponsor.
- **Laboratory Tests:** If central laboratory testing cannot be performed at the study site or via homecare visits, every attempt should be made to perform the protocol-required tests at a local laboratory. The results and reference ranges of all laboratory tests are to be sent to the Investigator and entered in to the eCRF. **Note:** *Investigational product can only be dispensed if central or local laboratory values are available.*
 - Minimum testing required to support the protocol: Total bilirubin, AST, ALT, INR, sodium and creatinine (for subjects past 4-week visit) and urine-based β -hCG pregnancy test.

- **Investigational Product Distribution:** Investigational product may be sent directly to the subject from either the study site or a third-party vendor via a courier service if subjects are not able to attend study site visits. Direct shipment of investigational product from the Investigator site to subjects must adhere to the site's institutional and pharmacy procedures and country specific requirements. If the Investigator is unable to evaluate safety and tolerability and assess the benefit-risk for the individual subject, the subject must interrupt investigational product until the assessment can be completed.
- **Home Visits:** If laboratory tests cannot be obtained from local laboratories, qualified home nursing support (where available and permitted) is an accepted option that may be employed to supplement telemedicine interactions to enable for the collection and processing of blood samples for laboratory tests including PK and PD samples, if required, and conduct other limited assessments (e.g., assessment of vital signs, completion of protocol required subject questionnaires).
- **Monitoring:** *There is an expectation that outside of extenuating circumstances, sites will be available for scheduled on-site monitoring.* Cancelling or postponing of on-site monitoring visits and extension of the period between monitoring visits may occur per specific local guidelines and regulations. Alternatively, additional off-site monitoring activities such as phone calls, video visits, emails may be used to discuss the trial with the Investigator and site staff. Remote source verification also may be performed if it is permissible by the local regulations.

Any other alternative procedures or assessments not listed above must be discussed with the Medical Monitor and documented by the Investigator, maintain subject participant confidentiality and be compliant with HIPPA/GDPR and 21 CFR Part 11 guidance.

In addition to regularly collected trial data, available COVID-19 related data such as COVID-19 testing will also be collected for all subjects. Any subject that contracts the sars-cov-2 virus should have this reported as an adverse event under the description "COVID-19" per Medical Dictionary for Regulatory Activities (MedDRA). If a subject is hospitalized for COVID-19 complications an SAE should be reported in accordance with the protocol and national requirements.

10.2. COVID-19 Vaccine

COVID-19 vaccination (with vaccines approved for emergency use in the country where you practice) is allowable for participants enrolled in this trial. Of note, as the currently approved COVID-19 vaccines have not been specifically tested in the NASH or PBC subject population, nor the pediatric population suffering from BA, there are no safety data available specific to use of COVID-19 vaccines in PBC, NASH subjects or in children suffering from BA.

If a subject receives a COVID-19 vaccination, the date(s) of vaccination(s), vaccine name, and manufacturer should be recorded as a concomitant medication for each dose.

11. INVESTIGATIONAL PRODUCT/STUDY MEDICATION MATERIALS AND MANAGEMENT

11.1. Investigational Products

11.1.1. Obeticholic Acid

The investigational product for OCA is supplied as a 5 mg as well as matching OCA placebo tablet with the same tablet appearance. OCA 5 mg and matching placebo tablets are white, round, 8-mm diameter, film-coated tablets debossed with “INT” on 1 side and “3547” on the other side and will be supplied throughout the study period. Each OCA 5 mg and placebo tablet contains the following inactive ingredients: [REDACTED]

The OCA 5 mg and matching placebo tablets will be provided for oral administration in high density-polyethylene bottles with heat induction seals and child-resistant closures, containing 100 tablets with desiccant. All OCA investigational product is manufactured according to Good Manufacturing Practices.

11.1.2. Bezafibrate

The investigational product for BZF is supplied as 100 mg and 200 mg IR tablets as well as a matching placebo tablet with the same tablet appearance. The BZF and matching placebo tablets are white, round, 10-mm diameter, film-coated tablets debossed with “G6” on 1 side and no markings on the other side and will be supplied throughout the study period. The BZF 400 mg IR dose will be achieved by taking 2 BZF 200 mg IR tablets. The BZF 100 mg and 200 mg IR tablets contain the following inactive ingredients: [REDACTED]

[REDACTED] The matching placebo contains the following inactive ingredients: [REDACTED]

Active BZF and matching placebo investigational product will be provided for oral administration in polyvinyl chloride blister packs sealed with aluminum foil. The blister packs will be assembled in weekly blister wallets that contain the appropriate active BZF dose (100 mg IR and 400 mg IR) for daily administration, depending on treatment arm. All BZF investigational product is manufactured according to Good Manufacturing Practices.

11.2. Investigational Product Packaging and Labeling

11.2.1. DB Phase

All OCA 5 mg and matching placebo investigational product for the DB treatment phase will be provided as tablets for oral administration in high density-polyethylene bottles with heat induction seals and child-resistant closures, containing 100 tablets and desiccant. The packaging and labeling will not reveal any information about the treatment dose contained in the bottles.

Active BZF and matching placebo investigational product will also be provided as tablets for oral administration for the DB Phase in polyvinyl chloride blister packs sealed with aluminum foil. The blister packs will be assembled in weekly blister wallets that contain the appropriate active BZF dose (100-mg IR and 400-mg IR) for daily administration, depending on treatment

arm. The blister packaging and labeling will not reveal any information about the treatment dose contained in the blister wallets. Each weekly blister wallet will contain 2 rows of 9 tablets, one for each day of the week plus 2 extras for contingency. Each row is specified with a number from 1 to 9. The subject should take 2 tablets, one from each row, from the blister wallet daily to achieve the appropriate treatment dose.

The OCA and BZF investigational product will be dispensed for oral administration in dosing kits that contain 1 bottle of OCA or placebo and weekly blister wallets that contain the active BZF dose (100 mg IR or 400 mg IR) or placebo. Kits will be dispensed to the subject according to the visit schedule in [Table 3](#) to provide sufficient tablets for daily dosing until the next time investigational product/study medication is dispensed. Each subject should take 3 tablets daily, 1 tablet from the OCA bottle and 2 tablets from the weekly BZF blister wallet (as described above), throughout the DB Phase.

The packaging and labeling of OCA and BZF investigational product supplies is performed according to Good Manufacturing Practice standards by a designated qualified vendor.

11.2.2. LTSE Phase

Subjects may transition to an LTSE phase of the study after the DB treatment phase. During the LTSE phase, subjects will receive treatment with the OCA 5 mg and BZF 400 mg IR (Treatment D of the DB Phase) for daily administration. The dosing kits used in the LTSE Phase of the study will be provided in a similar manner to those used in the DB Phase of the study. The OCA and BZF investigational product will be dispensed in dosing kits that contain 1 bottle of OCA 5 mg and weekly blister wallets that contain the BZF 400 mg IR dose. Dosing kits will be open labeled that include the OCA 5 mg and BZF 400 mg IR dose information. Kits will be dispensed to the subject according to the visit schedule in [Table 4](#) to provide sufficient tablets for daily dosing until the next time investigational product/study medication is dispensed. Each subject should take 3 tablets daily, 1 tablet from the OCA bottle and 2 tablets from the weekly BZF blister wallet, during the LTSE Phase.

11.3. Investigational Product/Study Medication Storage

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

11.4. Investigational Products Administration

Refer to [Section 9.1](#).

11.5. Investigational Product Accountability and Disposal

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

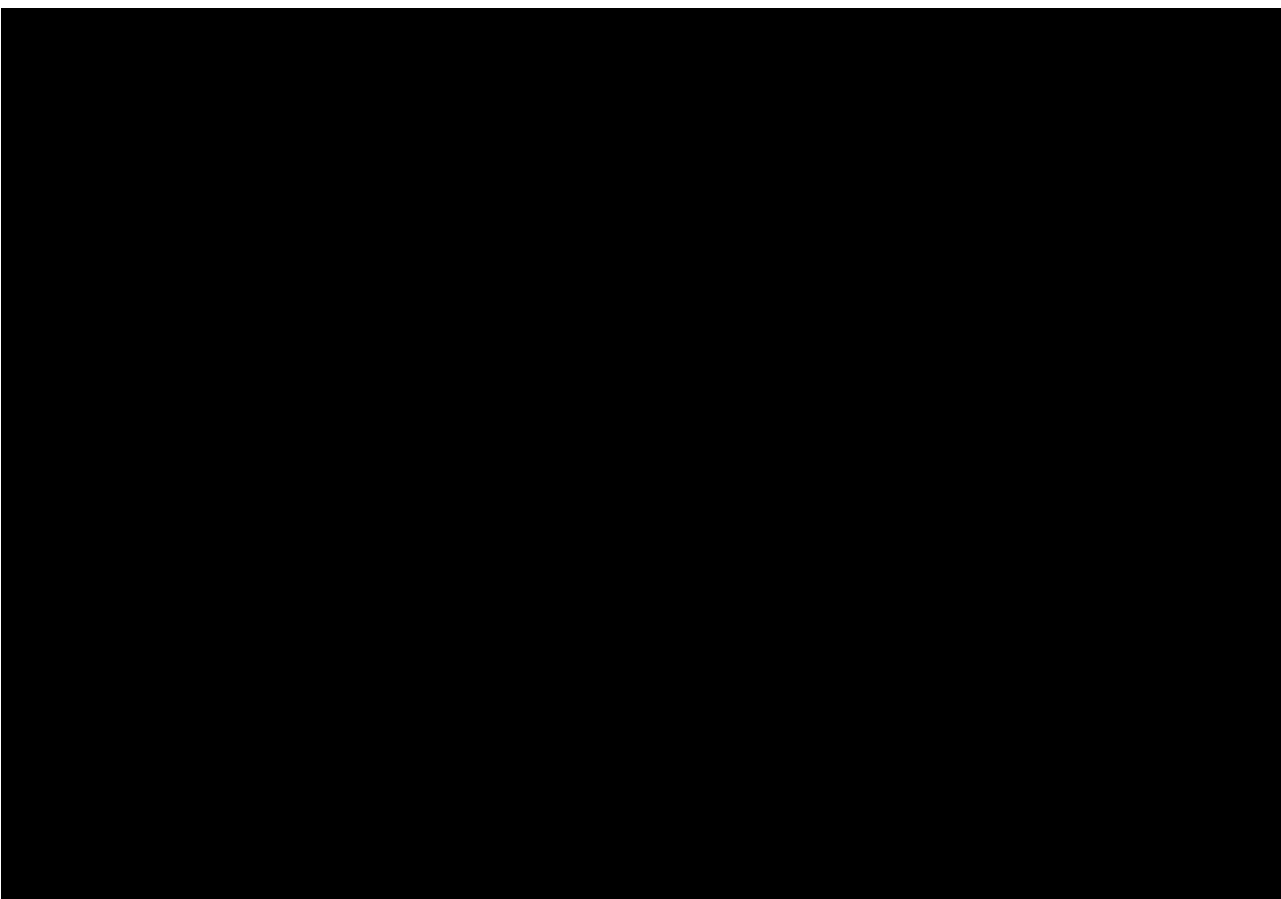
All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of study medication accountability, including records of individual subject dispensing and final return or disposition (as directed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

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

12. EFFICACY ASSESSMENTS

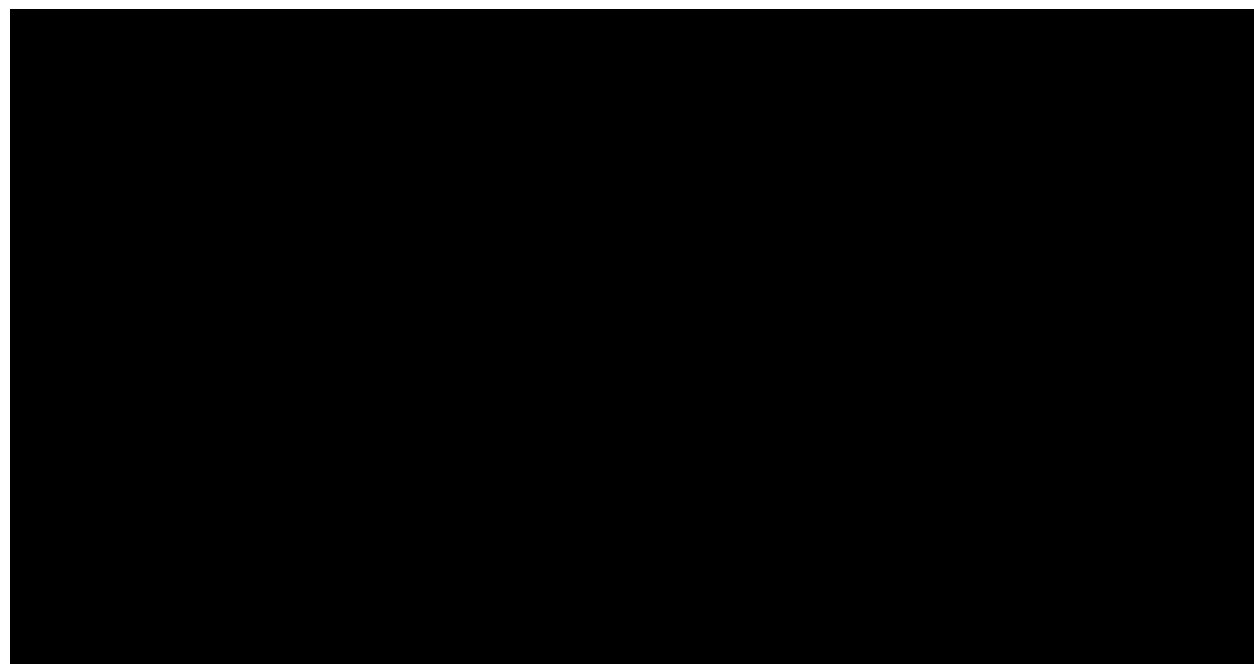
12.1. Efficacy Laboratory Assessments

Refer to [Table 16](#) for a full list of analytes to be tested. Laboratory assessments, including the primary endpoint, ALP, will be performed according to the schedule presented in [Table 3](#) and [Table 4](#) for the DB Phase and the LTSE Phase.



12.4. Prospective Screening for Gallbladder Diseases

Screening for gallbladder disease will consist of a detailed subject medical history and a baseline right upper quadrant ultrasound exam (if not performed within 3-month of the Screening Visit) to determine the presence of cholelithiasis and gallbladder disease. The diameter of the subject's common bile duct will be recorded as well as an alpha-fetoprotein (AFP) assessment according to the schedule presented in [Table 3](#). For subjects who develop gallbladder disease during the study, gallbladder disease screening assessments for study visits after onset of gallbladder disease are not required.



13.1. HepQuant-SHUNT Assessments

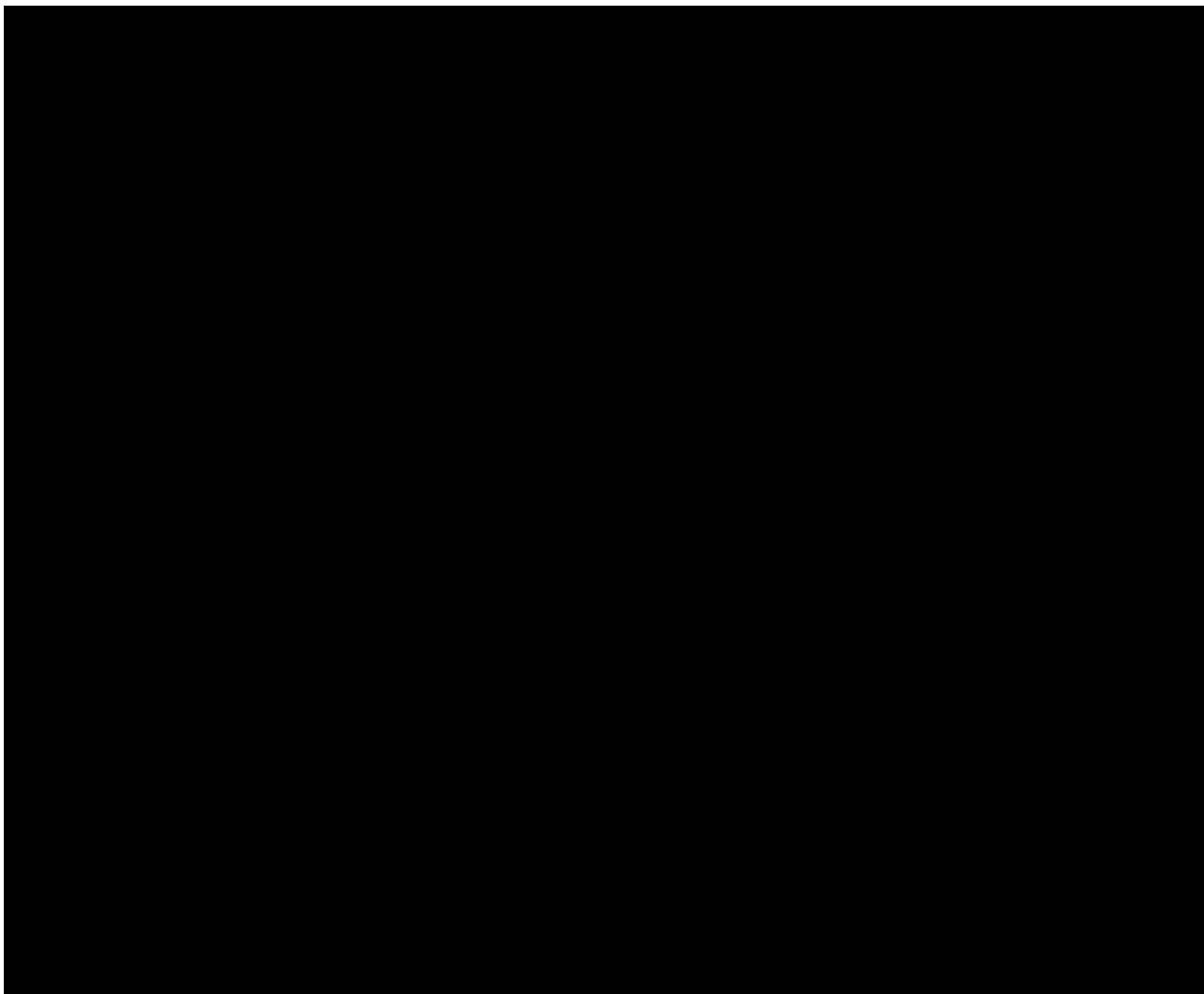
An assessment of liver function using the HepQuant-SHUNT assessment will be performed according to the schedule in Table 3 and Table 4.

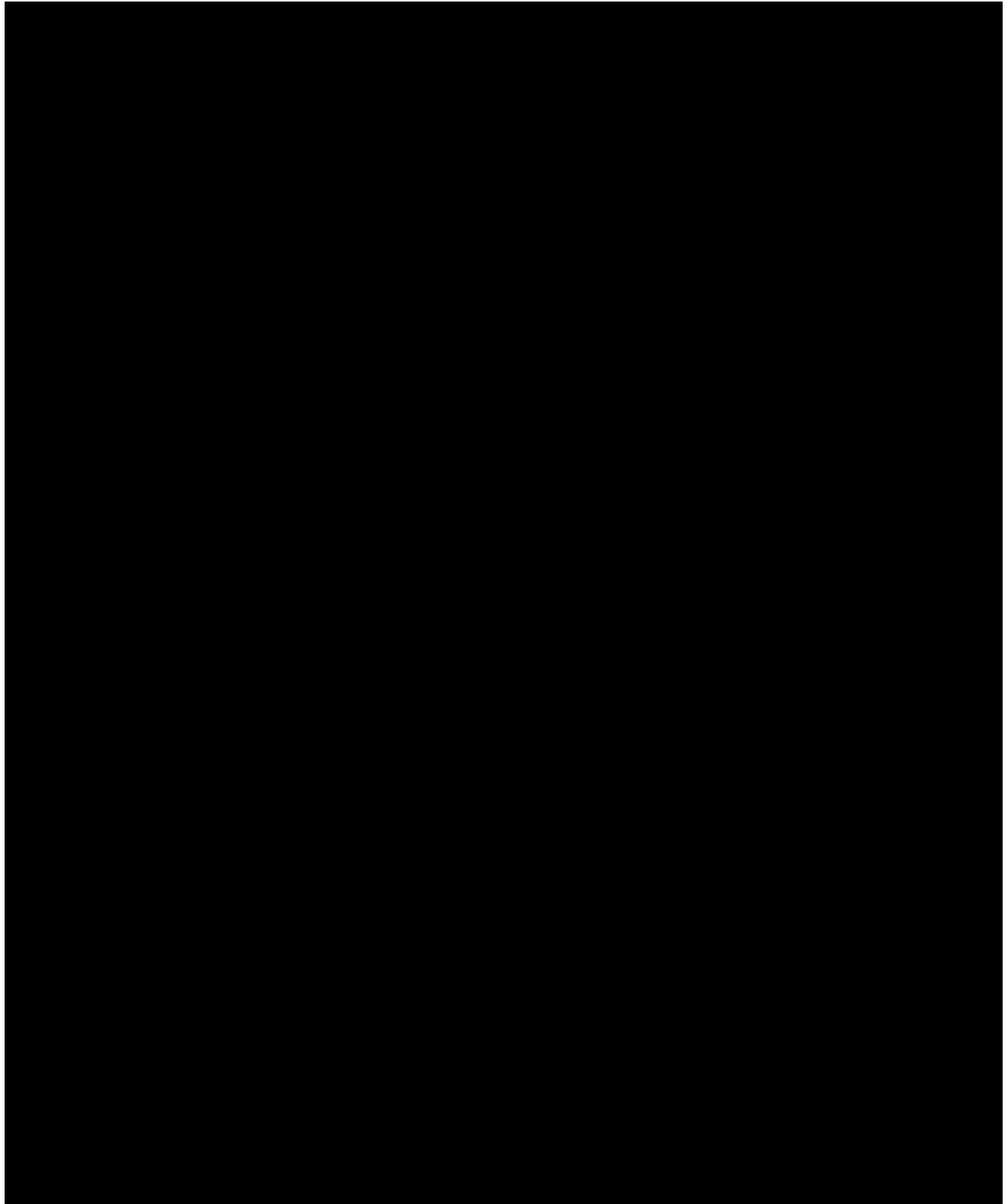
Detailed instructions for HepQuant-SHUNT testing will be described in a study operational manual (HepQuant SHUNT Test Instructions for Use). Of note, the test should not be administered if the diastolic blood pressure is 110 mmHg or higher. The test can be rescheduled once the blood pressure is controlled. Administration of β -blockers, angiotensin II receptor blockers, or angiotensin-converting enzyme inhibitors should be delayed on the morning of testing until after the SHUNT test administration. All subjects will be required to provide consent prior to participating.

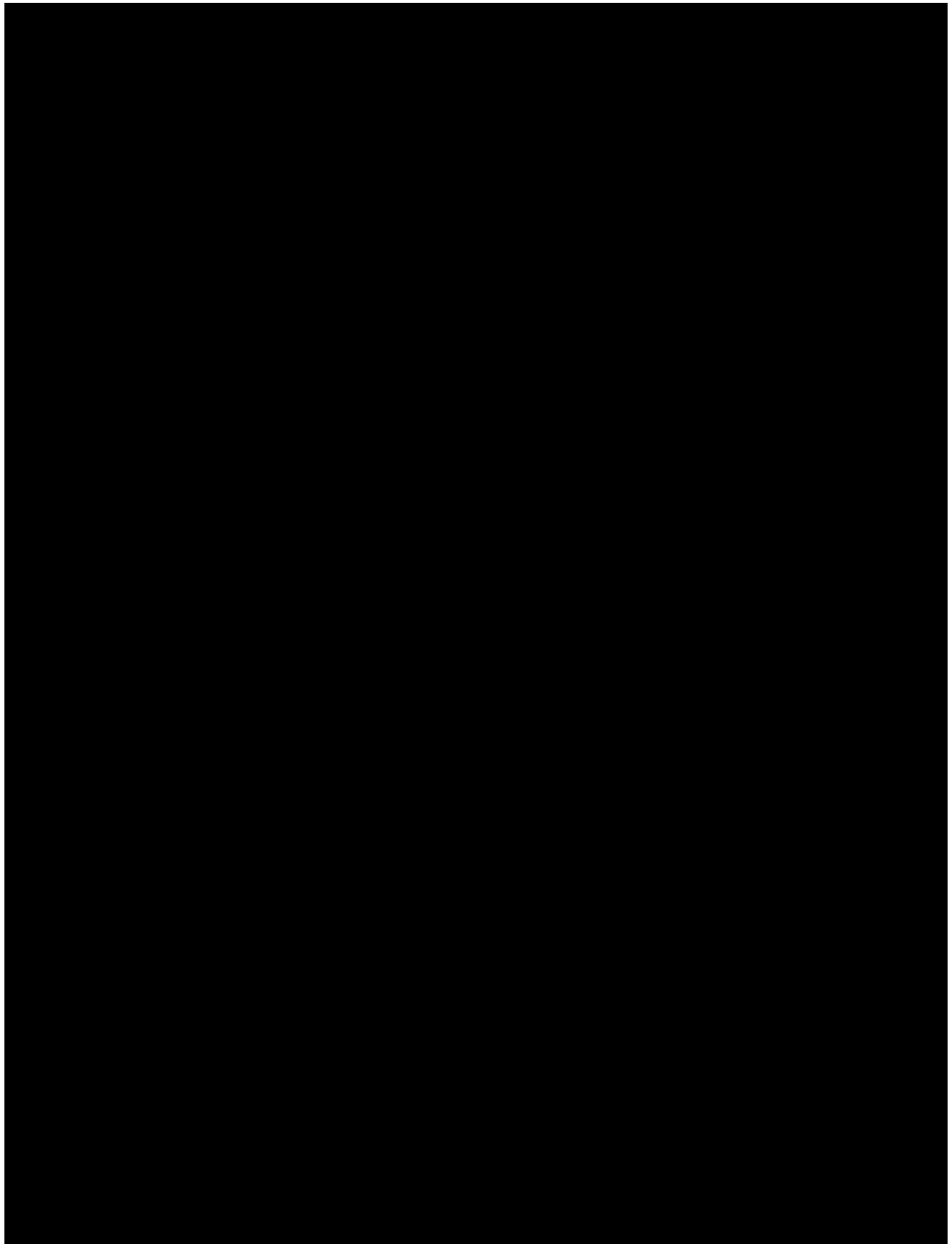
In brief, the test involves placement of an indwelling peripheral venous catheter (usually in the antecubital vein of the arm), an injection of 20 mg ^{13}C -cholate (cold, stable label, NOT RADIOACTIVE) intravenously, and a drink of flavored solution of 40 mg d4cholate (again, cold, stable label, NOT RADIOACTIVE). Blood samples will be taken at predose of cholate and 5, 20, 45, 60, 90 minutes post-dosing. Blood samples will be allowed to clot, spun, and serum transferred to transport tubes for mailing to HepQuant lab for processing and analysis. The HepQuant-SHUNT test will be used under an FDA investigational device

exemption in the US. HepQuant-SHUNT is a test being investigated as a potential quantitative measure of hepatic physiology and function. As liver disease progresses, from early stage with minimal stiffness to late-stage stiffness, cirrhosis, and clinical complications, hepatic function and the two circulatory inflows to the liver, systemic and portal, become increasingly impaired. The HepQuant-SHUNT test measures a liver-specific function, clearance of cholate, from both systemic and portal circulations simultaneously. The test is based on the fact that liver disease impairs function and alters the portal circulation. As blood flow to the liver becomes impaired a greater amount of the administered cholates escapes extraction by the liver and spills over into the systemic circulation. This is manifested as an increase in systemic cholate concentration in the blood samples obtained through the peripheral venous catheter. Complete details regarding the HepQuant SHUNT test and its use in this study can be found in [Appendix B](#).

14. CLINICAL PHARMACOLOGY ASSESSMENTS







15. SAFETY ASSESSMENTS

15.1. Adverse Events and Serious Adverse Events

AEs and SAEs will be handled in the same manner for both the DB Phase and the LTSE Phase.

15.1.1. Definitions of Adverse Events

15.1.1.1. Adverse Events

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

AEs include, but are not limited to, (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. For reporting purposes, pregnancy is not considered an AE, but must be reported expeditiously as described in [Section 15.1.9](#).

AEs should be elicited in a general way, without leading the subject or asking about the occurrence of any specific symptom.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms “sudden numbness, dizziness, and difficulty speaking.” The AE medical term of “stroke or cerebrovascular accident” should be recorded, as it more accurately describes the AE.

Subjects should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as pale-colored stools, urine color from pale to deep amber (dark), nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or whites of eyes, and bruising easily.

15.1.1.2. Serious Adverse Event

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

- Death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Any malignancy is to be reported as a serious AE.

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

15.1.1.3. Treatment-Emergent Adverse Events

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

15.1.1.4. Adverse Events of Special Interest

The following are considered AEs of special interest:

- Pruritus
- Hepatic injury
- Myalgia
- Renal impairment

15.1.1.5. Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as a suspected adverse reaction which is assessed as serious, causally related to the investigational product, and unexpected per the reference safety information (RSI) in the Investigator's Brochure.

SUSARs are subject to expedited reporting. The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the relevant competent authorities (either directly or through the EudraVigilance Clinical Trials Module, as applicable), and to the Ethics Committees, no later than seven days after knowledge by the Sponsor of such a case.

Relevant follow-up information is subsequently communicated within an additional eight days, unless required differently by local laws and regulations. All other SUSARs shall be reported to

the competent authorities concerned (either directly or through the EudraVigilance Clinical Trials Module) and to the Ethics Committees concerned, within a maximum of fifteen days of first knowledge by the Sponsor.

The Sponsor shall also inform all participating investigators, as applicable to the local regulations.

15.1.2. Relationship to Treatment Regimen

The Investigator will document her/his medical opinion on the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 12. 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 that there is evidence to suggest a causal relationship between the investigational product and the AE.

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

Table 12: Relationship of Adverse Events to Treatment Regimen

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the IP or in which the IP level has been established in body fluids or tissue, that follows a known or expected response pattern to the suspected IP, and that is confirmed by improvement on stopping or reducing the dosage of the IP and reappearance of the reaction on repeated exposure
Probable	A reaction that follows a reasonable temporal sequence from administration of the IP, that follows a known or expected response pattern to the suspected IP, that is confirmed by stopping or reducing the dosage of the IP, 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 IP and that follows a known or expected response pattern to the suspected IP but that could readily be produced by several other factors
Unlikely	A reaction that does not follow a reasonable temporal sequence from administration of the IP, that does not follow a known or suspected response pattern to the suspected IP, 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

15.1.3. Relationship to Study Procedures

The Investigator will document her/his opinion of the relationship of the AE to study procedures using the criteria outlined in Table 13.

Table 13: Relationship of Adverse Events to Study Procedures

Relationship	Description
Related	A reaction that follows a reasonable temporal sequence from the HepQuant-SHUNT procedure or other study procedures; that follows a known or expected response pattern to the administration of cholate or collection of blood samples.
Not Related	Any event that does not meet the above criteria.

15.1.4. Recording Adverse Event Severity

AEs must be graded for severity (i.e., intensity). A severity category of mild, moderate, or severe, as defined in Table 14, must be entered on the AE eCRF. It should be noted that the term “severe” used to grade intensity is not synonymous with the term “serious.” The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 14: Severity of Adverse Events

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

15.1.4.1. Severity of Pruritus (as an Adverse Event)

To ensure consistency in reporting, pruritus AEs must be graded for severity (i.e., intensity). As pruritus is a subjective symptom, clinical judgment should be used to determine its severity and management, as shown in Table 15. To assess the potential improvement in pruritus with treatment, baseline pruritus presence (yes/no) and severity (as shown in Table 15) will be determined.

Table 15: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus and Medical Intervention
1 = Mild	Mild or localized; topical intervention indicated
2 = Moderate	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living
3 = Severe	Intense or widespread; constant; limiting self-care activities of daily living or sleep; oral corticosteroid or immunosuppressive therapy indicated

Since pruritus is a subjective symptom and the occurrence and magnitude of which are not readily measured by objective tools, clinical judgment needs to be applied in the management of each subject. Managing OCA-related pruritus may help improve tolerance in those subjects who experience CS pruritus and may otherwise discontinue from the study prematurely. General guidance for the management of subjects experiencing significant pruritus includes the following:

- **Drug holiday:** A drug holiday is defined as an Investigator’s “prescribed” complete interruption of dosing for 1 or more consecutive days (i.e., nondaily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the eCRF. Per [Section 8.2.1.1](#), subjects with pruritus $\geq$ Grade 3 in severity and possibly, probably, or definitely related to the investigational product must discontinue investigational product but are encouraged to continue study visits. If the drug holiday lasts more than 30 days in the DB or LTSE Phase, the subject should be withdrawn from the study.

- Prescribing BAS (see [Section 9.2.5](#)): Subjects taking BAS (including cholestyramine and its derivatives, colestipol, colesevelam, or other BAS) should be instructed to not to take these medicines during conduct of the study.
- Other therapies may be tried as deemed clinically appropriate.
- Less frequent dosing of investigational product (e.g., on alternate days) may be administered, after which, subjects may return to their original daily dose as soon as tolerated.

15.1.5. Reporting of Adverse Events and Serious Adverse Events

15.1.5.1. Reporting of Adverse Events

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

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

In addition, the Investigator should contact the study Medical Monitor upon awareness when any signs or symptoms of hepatic decompensation are observed in any subject.

15.1.5.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

All SAEs must be immediately reported (i.e., within 24 hours of awareness) 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 SAE. In the event that the EDC system is inaccessible, an SAE may be reported by:

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

If an SAE is initially reported by e-mail or fax, SAEs must also be entered 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 either investigational product. The Sponsor will also assess whether the event is causally related to either

investigational product, in addition to assessing the overall safety profiles of both investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators (where required) of Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to +1 800 497 8521 or e-mailed to sae@interceptpharma.com as soon as possible. Redacted medical record source documentation will be requested for all SAEs.

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

Additional Investigator Responsibilities for SAEs

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

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

15.1.6. Notification of Post-Treatment SAEs for Subjects who Continue in the Study

Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in [Section 15.1.5.2](#).

15.1.7. Notification of Post-Study SAEs

All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in [Section 15.1.5.2](#).

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (i.e., within 24 hours) by following the instructions provided in [Section 15.1.5.2](#).

15.1.8. Follow-Up of AEs and SAEs

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

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

Drug-Induced Liver Injury or Disease Progression

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

Cholecystitis or Pancreatitis

Refer to [Section 12.4](#) for Ultrasound Screening for Gallbladder disease.

During the study duration, subjects will be instructed to contact the investigational site if they experience any of the following signs and symptoms: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever, and chills, worsening or new fatigue, or weakness. Subjects will also be counseled to seek immediate medical assistance if they experience persistent severe abdominal pain.

If a subject is suspected to have acute pancreatitis or develops signs and symptoms consistent with acute pancreatitis, amylase and lipase levels should be monitored for 3 months after the onset of symptoms per standard of care. The Investigator should contact the Medical Monitor upon awareness. Results should be recorded promptly in the eCRF. Investigators should refer to standard-of-care guidelines on suspected pancreatitis ([Banks 2013](#), [Greenburg 2016](#)). Diagnosis of acute pancreatitis includes at least 2 of the following:

- Abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back)
- Serum lipase activity (or amylase) at least 3 times greater than the upper limit of normal
- Characteristic findings of acute pancreatitis on computed tomography or magnetic resonance imaging

If a subject experiences signs and symptoms consistent with cholelithiasis and/or cholecystitis, the subject should be managed and monitored as described in [Section 7.5](#). The Investigator should contact the Medical Monitor upon awareness. Results should be recorded promptly in the eCRF.

15.1.9. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study, she must discontinue treatment with investigational product immediately (see [Section 8.2.1.2](#)) and the Sponsor must be notified

within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy eCRF in the EDC system and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to sae@interceptpharma.com or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in [Section 15.1.5](#) must also be followed.

15.2. Other Safety Parameters

15.2.2. Medical/PBC History/Demographics

Smoking and alcohol consumption history and current habits will be recorded. Alcohol consumption abstinence is recommended prior to PK visits during the DB and LTSE Phase. All demographic characteristics (age, sex, race, and ethnicity) will be recorded. Baseline pruritus by severity will be obtained on Day 1.

15.2.3. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the visits specified in the Schedule of Study Procedures (Table 3 and Table 4).

A basic physical examination should be performed, including all body systems pertinent to the subject. Any CS abnormality should be reported as an AE.

The physical examination must include the following:

- General appearance
- Skin

- Head, eyes, ears, nose, and throat
- Neck
- Lymph nodes
- Chest/respiratory system
- Cardiovascular system
- Abdominal region
- Extremities
- Musculoskeletal system
- Mental status
- Neurological system

15.2.4. Child-Pugh Classification

CP Assessment: The CP score is used to assess the prognosis of chronic liver disease in subjects with cirrhosis (Pugh 1973, Lucey 1997). CP Score will be assessed for all subjects during each clinic visit to proactively monitor for potential hepatic injury, disease progression, and/or hepatic decompensation. Scores will be recorded on the eCRF.

15.2.5. Vital Signs

Vital signs, height, and weight will be assessed at the visits as specified in Table 3 and Table 4. Vital signs taken will include oral temperature, sitting heart rate, respiratory rate, and seated blood pressure. When taking heart rate, respiratory rate, and blood pressure readings, subjects should be seated quietly for a minimum of 3 minutes before the readings are taken. Any CS abnormality should be recorded as an AE.

15.2.6. Electrocardiogram

Standard 12-lead ECGs will be collected as specified in Table 3 and Table 4.

All ECGs should be performed after at least 5 minutes of supine rest and before blood is collected. The 12-lead ECG results will be reviewed by the Investigator or designee, and findings will be recorded in the eCRF as normal, abnormal but not clinically significant (NCS) or abnormal and CS. Any CS abnormality on ECGs should be reported as an AE.

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the Investigator.

Investigative sites must retain a copy of all 12-lead ECGs. These ECGs must be clearly labeled with the subject ID number, date, and time.

15.2.7. Ultrasound Screening

During the DB Phase, an ultrasound exam of the right upper quadrant (RUQ) will be performed at screening to assess for cholelithiasis and gallbladder disease. The diameter of the subject's

common bile duct will be recorded. If gallbladder disease is detected, subjects' eligibility will be based on Exclusion Criterion #6 ([Section 8.1.2](#)).

The gallbladder ultrasound will be performed under fasting conditions.

15.2.8. Laboratory Assessments

Except for Screening Visit 1, subjects will be instructed to attend each study visit in a fasted state, preferably in the morning, and subjects should remain fasted until their blood samples have been collected. For visits that require fasting, the Investigator or designee will verify that the subject has fasted for at least 8 hours. The fasting status will be recorded in the source and eCRF. If the subject reports having eaten or drunk anything other than water within 8 hours, the Investigator or designee will document accordingly and remind the subject that fasting is required before all study visits.

Blood and urine samples for laboratory assessments will be collected at the visits specified in [Table 3](#) and [Table 4](#).

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

All subjects with laboratory tests containing CS abnormal values are to be followed regularly until the values return to normal ranges, until a valid reason (other than investigational product related AE) is identified, or until further follow-up is deemed medically unnecessary. Clinically significant changes as assessed by the Investigator in laboratory tests, not associated with a documented AE, should be recorded as AEs. An abnormal laboratory value should be deemed clinically significant if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, for example change of dose, discontinuation of drug, close observation, more frequent follow-up assessments, or further diagnostic evaluation.

Urine-based beta-human chorionic gonadotropin (β -hCG) pregnancy tests will be performed in female subjects of childbearing potential per protocol-specified visits. If a urine pregnancy test is positive, a serum pregnancy (serum quantitative β -hCG 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 15.1.9](#) until pregnancy outcome.

All additional biomarkers of disease severity and blood samples (including lipid panel) collected for additional biomarker analysis will be stored for up to 1 year after the end of the study and destroyed if not analyzed.

CP and [REDACTED] will be calculated based on demographic, examination, and clinical laboratory values as described in the statistical analysis plan (SAP).

Blood samples for determining the plasma concentrations of OCA and BZF and their metabolites will be collected in this study.

Laboratory analyte results may be used to calculate various cardiovascular risk and stiffness measurement scores.

The list of laboratory analytes to be tested is shown in Table 16.

Table 16: List of Laboratory Scores and Analytes

Laboratory Assessment	Scores and Analytes ^a
Serum chemistry	Albumin, BUN, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), ALP, GGT, electrolytes (calcium, chloride, potassium, sodium), glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, free fatty acids, eGFR, and CK
Hematology	Hemoglobin, hematocrit, white blood count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets, and red blood cell count (including MCV, MCH, MCHC)
Urinalysis	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, microscopic exam, creatinine, albumin, leukocytes, nitrates, and albumin/creatinine ratio (if positive)
Coagulation	PT, aPTT, INR
Thyroid function tests	Free T3, free T4, and TSH
Virology	hBsAg, HCV
Pregnancy test (female subjects of childbearing potential) ^b	β-hCG

ALP = alkaline phosphatase; ALT = alanine aminotransferase; [REDACTED]; aPTT = partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; [REDACTED]; C4 = 7α-hydroxy-4-cholesten-3-one; [REDACTED]; CK = creatine kinase; [REDACTED]; GGT = gamma-glutamyl transferase; hBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; LDL=low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; OCA = obeticholic acid; [REDACTED]; PT = prothrombin time; T3 = triiodothyronine; T4 = thyroxine; [REDACTED]; TSH = thyroid-stimulating hormone; TG = triglycerides; VLDL = very low density lipoprotein

^a Overlapping analytes will be analyzed only once (with exception of ALP total for calculation of isoenzymes).

^b Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol-specified visits. If a urine pregnancy test is positive, a serum pregnancy (serum quantitative β-hCG) test must be performed to confirm the result. If positive, the Sponsor must be notified, and the subject will be followed through pregnancy outcome, as outlined in [Section 15.1.9](#).

^c Where available

^d For subjects who have consented

15.2.9. Health-Related Quality of Life

See [Section 12.2](#) for questionnaires to be used.

15.3. Data Monitoring Committee

The DMC is an independent committee that includes hepatologists, physicians, epidemiology/cardiology expert(s), and statistician(s) who will not be involved in the study as Investigators, adjudication committee members, or consultants. The independent DMC will review safety data during the conduct of the trial. In addition to the periodic review of safety data, the results of the interim analysis will also be reviewed by the DMC.

The DMC will have oversight over the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs.

The DMC will meet approximately quarterly at scheduled meetings, and ad hoc meetings will be convened, as appropriate. Based on review of these data, the DMC will advise the Sponsor on the validity and scientific merit of continuing the study.

Written minutes of both the open and closed DMC sessions will be prepared.

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

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

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

Data flow, access, process, and disclosure will be described in a Data Access Plan. The Data Access Plan will cover the process by which an independent statistical group will conduct analyses and provide to the DMC, including the interim analyses to support regulatory interactions.

15.4. Hepatic Safety Adjudication Committee

All potential events of hepatic injury will be adjudicated in all enrolled subjects that occur after administration of the first dose of investigational products during the double-blind and LTSE phase. Potential events of hepatic injury will be reviewed by the blinded Hepatic Safety Adjudication Committee (HSAC).

Specific details of the events that will be adjudicated are described in the respective adjudication charter. Any changes to either the adjudication process or changes to specific events to be adjudicated will be addressed in the charters and will be communicated to all study sites outside of a protocol amendment.

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

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

16. STATISTICS

An SAP providing details regarding the specific planned analyses will be prepared and finalized before study database lock and unblinding of the study. The SAP will be prepared as soon as planning for the statistical methods section of the protocol is initiated. The SAP will be approved prior to database lock and unblinding of the study.

16.1. Analysis Populations

ITT Population:

The Intent-to-Treat (ITT) Population will include all randomized subjects. Treatment assignment will be based on the randomized treatment.

mITT Population:

The modified ITT (mITT) Population will include all randomized subjects who have baseline and at least one post baseline ALP assessment. Treatment assignment will be based on the randomized treatment.

Safety Population:

The Safety Population will include all randomized subjects who receive at least 1 dose of BZF and/or OCA. Treatment assignment will be based on the actual treatment received.

LTSE Population:

The LTSE Population will include all subjects who receive at least 1 dose of investigational product, during the LTSE phase.

16.2. Determination of Sample Size

According to [Corpechot 2018](#), the median percent change from baseline in ALP at Month 24 of BZF 400 mg is -60% (i.e., -146 U/L) with an interquartile range (IQR) from -66% to -46% based on 46 subjects. The data from Month 24 is used in the sample size calculation with the assumption that ALP is stable from Month 3 to Month 24. In Study 747-301, the standard deviation of change from baseline of ALP at Month 3 is 74 based on 69 subjects. The pooled standard deviation of change from baseline at Month 3 based on those two treatments is 58. Assuming the change from baseline of ALP in BZF is -146 U/L, 15 subjects per arm will provide 80% power to detect a treatment difference of 60 U/L between BZF arm and BZF+OCA arm at two-sided alpha of 0.05 with the pooled standard deviation of 58.

16.3. Primary Efficacy Analysis in Double-Blind Phase

The Primary Efficacy Analysis for the DB Phase, the change in ALP from baseline to Week 12, will be conducted using the mITT Population when all subjects have completed the DB treatment phase.

The intercurrent event in this study includes the use of prohibited medication (see [Section 9.2](#)) and treatment discontinuation. For the analysis on the primary efficacy endpoint, data collected after the intercurrent events, such as the use of prohibited medications, and data collected after treatment discontinuation, will not be included.

Analyses of change in ALP will be carried out using a mixed-effect repeated measures model (MMRM) to evaluate the effect of treatment groups over time. The dependent variable will be the change in ALP from baseline. The model will include the terms of treatment group, visit, treatment by visit interaction, and randomization stratification variables as factors and the baseline value as a covariate.

In addition, a supportive analysis using the mITT Population will be performed on the primary efficacy endpoint, where data collected after the intercurrent events will be included in the analysis. This provides the evaluation of efficacy effect regardless of treatment adherence.

16.4. Secondary and Additional Efficacy Analyses for the Double-Blind Phase

The ITT Population, e.g., all randomized subjects, will be the primary population used for the secondary and additional efficacy analyses.

The secondary endpoints include:

- The response rates of $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ reduction from baseline at Week 12, and normalization rates of ALP at Week 12
- Normalization rates at Week 12 of GGT, ALT, AST, ALP, total and conjugated bilirubin, and lipid panel
- Change from baseline to Week 12 in GGT, ALT, AST, and total and conjugated bilirubin, and lipid panel
- Change from baseline to Week 12 in 7 α -hydroxy-4-cholesten-3-one (C4) and bile acids

[REDACTED]

For the secondary and [REDACTED]

[REDACTED]

All continuous and categorical secondary and [REDACTED]

[REDACTED]

Analyses for ALP response rates of $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ reduction from baseline at Week 12, and normalization rates and percentage of subjects with ALP $< 1.67 \times$ ULN and total bilirubin $\leq$ ULN and ALP decrease of $\geq 15\%$ from baseline will be performed using a Cochran-Mantel-Haenszel test stratified by the randomization stratification factor.

For the rolling interim analysis (described below in the interim analyses [Section 16.7](#)), if data are insufficient for the MMRM model or the Cochran-Mantel-Haenszel test, a simpler model or test may be used.

[REDACTED]

[REDACTED]

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

[REDACTED]

16.7. Interim Analyses

The Sponsor will use data output from interim analyses from the DB phase for purposes of regulatory interactions and subsequent Phase 3 trial design planning. The SAP will specify the methods for the interim analyses, as well as additional details on the conduct.

Rolling Interim Analysis

The Sponsor will perform an unblinded rolling analysis of efficacy, PK, and safety data throughout the DB phase. Details of the unblinding and Data Access Plan, including Sponsor Staff that will be unblinded, will be provided in separate documents. All PIs and site staff and patients will remain blinded throughout the study.

The efficacy measures for the rolling interim analysis include:

- Primary Endpoint: The change in ALP from baseline to Week 12 in the DB Phase in the mITT Population
- Secondary Endpoints:
 - The ALP response rates of $\geq 10\%$, $\geq 20\%$, $\geq 30\%$, and $\geq 40\%$ reduction from baseline at Week 12 and the normalization rates of ALP at Week 12 in ITT Population
 - The changes from baseline to Week 12 in GGT, ALT, AST, total bilirubin, and conjugated bilirubin, and lipid panel in ITT Population

In addition, analyses of drug exposure and safety assessments will be performed.

DMC Interim Safety Analysis

The DMC will perform an interim safety analysis when approximately 32 subjects complete the Week 12 visit in accordance with the DMC Charter. The DMC will review the interim criterion for safety data and other relevant information to determine whether to recommend and continue the study.

16.8. Handling of Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination. Missing data will be assumed to be missing at random. No data will be imputed.

16.9. Safety Analyses

The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.

Safety data, including SAEs, TEAEs, physical examinations, ECGs, vital signs, clinical laboratory assessments, and treatment discontinuations, will be compared across all treatment groups during the treatment phase.

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

Laboratory parameters and vital signs will be summarized (including Hy's law) by treatment group using descriptive statistics at baseline and at each scheduled postbaseline 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 before treatment.

16.9.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term for each treatment group and by severity and relationship to treatment. Summaries of TEAEs leading to investigational product discontinuation and SAEs will be provided. Adverse events of special interest as described in [Section 15.1.1.4](#) will be summarized for each treatment group.

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

16.9.2. Adjudicated Hepatic Injury Events

Hepatic injury events are included in the HSAC for adjudication.

Adjudicated hepatic injury events is a binary endpoint and will be summarized for the Safety Population.

Descriptive statistics will be presented. Treatment groups will be compared using the Cochran Mantel Haenszel test stratified by the randomization stratification factors. For subjects with more than one event, the subjects will be counted only once in the analyses.

16.9.3. Clinical Laboratory Evaluations

Laboratory parameters and vital signs will be summarized (including Hy's law) by treatment group using descriptive statistics at baseline and at each scheduled postbaseline 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 before treatment (except for lipoprotein assessments where baseline will be Day 1).

In addition, shift tables from baseline based on normal ranges will be provided for hematology, coagulation, and serum chemistry by treatment group to assess changes in laboratory values from baseline to each on-study evaluation.

16.10. Data Management

To ensure the quality of clinical data across all subjects and sites, Intercept's Data Management or its designee will perform data review on a regular basis throughout the conduct of a study in accordance to the study's Data Management Plan (DMP). Data Management Review is performed on an ongoing basis throughout the project. Queries are posted accordingly and resolved/closed in a timely manner. Special focus to critical safety and efficacy variables is given prior to any milestone being completed. Reconciliation of SAEs between the clinical and safety databases will be performed by Intercept's Data Management or designee.

A start-up training presentation is conducted at the Investigator kick-off meeting wherein Investigators and site coordinators are trained on different aspects of the web-based EDC system and completion of the eCRF. Data Management also creates instructional material (such as eCRF Completion Guidelines) which is made available to the study sites.

Access to the EDC system will be granted once the system-specific user role training has been successfully completed. eCRF data will be encoded and stored in a clinical trial database. Edit checks, which are part of the data validation process, and safety alerts will be programmed in the EDC application to detect data errors and safety signals. Corrections to data collected in eCRFs will be automatically documented through the audit trail of the EDC system which is 21 CFR Part 11 compliant.

Any data for which paper documentation is provided by the subject (such as paper diary to collect Subject Reported Outcomes measures) will serve as the source document and will be retained by each site. Central laboratory data or non-eCRF data (such as ECG, biomarker, imaging, PK/PD, etc.) will be uploaded to a secured sFTP site as stated in the respective Data Transfer Agreements.

17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

17.1. Study Monitoring

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

In order to perform this role, the CRA must perform source data verification and as such must be given access to the subject's primary source documentation (e.g., paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization

numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc.) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

17.2. Audits and Inspections

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

18. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see [Section 17.2](#) for more details regarding the audit process.

19. ETHICS

19.1. Ethics Review

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

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

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product,

according to local regulations and guidelines. The Sponsor will provide this information to the Investigator.

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

19.2. Ethical Conduct of the Study

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

19.3. Written Informed Consent

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

The subject's signed and dated ICFs must be obtained before conducting any study procedures.

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

19.4. Subject Confidentiality and Data Protection

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

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

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

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

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

20. INVESTIGATOR OBLIGATIONS

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

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

20.1. Adverse Event Reporting

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

20.2. Protocol Deviations

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

20.3. Regulatory Documentation

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

- Approved ICFs (all versions)
- IRB/IEC approvals (of protocol/amendments, subject questionnaires, etc.)
- Form FDA 1572 or equivalent form for the Investigator's region
- Current medical license of Investigators
- Curriculum vitae of Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

20.4. Ethics Review (IRB/IEC)

Please see [Section 19.1](#) for the Investigator's responsibilities regarding ethics review.

20.5. Archiving and Record Retention

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

All documents relating to the study including the ISF itself, source documents and subject medical files (retained per country specific regulations), completed study subject log, and confidential subject identification list will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor before the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

21. PUBLICATION POLICY

The Sponsor intends to publish the results of all clinical studies that it sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (<http://www.icmje.org>).

Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

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

- Clinical Trial Registries (e.g., www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (e.g., basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers, and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.

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

22. LIST OF REFERENCES

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APPENDIX A. PUBLICATIONS REPORTING SAFETY AND EFFICACY OUTCOMES FOLLOWING BEZAFIBRATE THERAPY

Reference	Type of Study, Analysis, or Review
Agrawal 2019	Meta-analysis of randomized controlled trials of BZF and UDCA in 369 patients with PBC
Akbar 2005	Pilot study of BZF 400 mg/day in 16 subjects with PBC to evaluate therapeutic efficacy of decreased nitrite production by BZF
Chung 2019	Placebo-controlled pilot study of additional fibrate treatment including BZF 400 mg/day in 29 subjects with UDCA-refractory PBC
Corpechot 2018	Double-blind placebo-controlled study of BZF 400 mg/day in 100 adult subjects with PBC with inadequate response to UDCA monotherapy
Feng 2019	Meta-analysis of UDCA + BZF 400 mg/day in 465 subjects with refractory PBC
Hazzan and Tur-Kaspa 2010	Pilot study using BZF 400 mg/day in 8 subjects with PBC following incomplete response to UDCA. Patients were followed for up to 110 months.
Honda 2013	In vitro study exploring the anticholestatic mechanisms of BZF by analyzing serum lipid biomarkers in 31 subjects with PBC patients and by cell-based enzymatic and gene expression assays
Honda 2019	Retrospective study of BZF 400 mg/day in 118 subjects with PBC followed for 1 year
Hosonuma 2015	Prospective multicenter randomized study of long-term combination therapy using UDCA and BZF 400 mg/day in 27 subjects with PBC and inadequate response to UDCA monotherapy
Itakura 2004	Prospective, randomized, crossover study of UDCA + BZF in 16 subjects with PBC
Iwasaki 1999	Single-arm clinical study of BZF 400 mg/day in 11 subjects with pre-cirrhotic PBC
Iwasaki 2008	Two prospective, multicenter studies of the efficacy of UDCA + BFZ 400 mg/day in 55 female subjects with PBC
Kanda 2003	Pilot study of UDCA + BZF 400 mg/day in 22 subjects with PBC nonresponsive to UDCA monotherapy
Ledermann 1981	Comparative pharmacokinetics of 400 mg bezafibrate after a single oral administration of a new slow-release preparation and the currently available commercial form in 17 subjects
Lens 2014	Pilot study, open-label single-arm clinical study of BZF 400 mg/day in 30 female subjects with PBC treated with UDCA who had abnormal alkaline phosphatase levels
Mizuno 2015	Single-arm clinical study of BZF 400 mg/day in 15 subjects with primary sclerosing cholangitis

Reference	Type of Study, Analysis, or Review
Nakai 2000	Preliminary study of Nakai of BZF using 400 mg/day in 10 subjects with PBC refractory to UDCA
Reig 2018	Single-arm study of 48 patients with PBC who had failed to respond adequately to UDCA treated with of BZF 400 mg/day
Takeuchi 2011	Prospective study of BZF using 400 mg/day in 37 subjects with PBC refractory to UDCA
Tanaka 2015	Multicenter, retrospective cohort study assessing long-term outcomes in 1121 subjects on BZF 400 mg/day and UDCA compared to UDCA monotherapy
Tanaka 2021	Multicenter, retrospective cohort study assessing survival rates in subjects on UDCA with (746 subjects) or without BZF (3908 subjects)
Yin 2015	Meta-analysis of randomized controlled trials assessing the efficacy of BZF 400 mg/day + UDCA (125 subjects) compared with UDCA monotherapy in subjects with PBC. Nine trials, with a total of 269 patients, were included in the analysis.

APPENDIX B. HEPQUANT-SHUNT TO MEASURE LIVER FUNCTION TO ASSESS LIVER DISEASE AND TREATMENT EFFECTS

The HepQuant SHUNT test is an investigational assay that has been included as an additional study objective. This Appendix describes the HepQuant SHUNT test and its use for assessing liver disease and treatment effects in this study.

HepQuant Contact Information: [REDACTED], MD

Background

The HepQuant SHUNT test could potentially fulfill an unmet medical need as a noninvasive test of global liver function and physiology. With progression, liver diseases alter hepatocyte function and the portal circulation which manifests as portal hypertension and portal-systemic shunting. The clinical consequences are coagulopathy, jaundice, varices, ascites, and encephalopathy. HepQuant SHUNT quantifies the changes in liver function and the portal circulation from early through late stages of disease.

Hepatic inflammation and hepatic fibrosis impair hepatocyte function and hepatic perfusion. Evolution to cirrhosis is associated with increasing hepatic impairment – ultimately leading to portal hypertension and portal-systemic shunting. Hepatocellular impairment, portal circulatory changes, portal hypertension, and portal-systemic shunting account for the major clinical manifestations of cirrhosis – jaundice, coagulopathy, fluid retention, varices and encephalopathy.

Underlying portal hypertension (PH) is a risk factor for poor outcome in liver disease. PH can be measured by threading a catheter from the jugular vein into the portal vein to measure the hepatic venous pressure gradient (HVPG). Increased HVPG correlates with risk of cirrhosis, varices, ascites, and decompensation ([Samonakis 2007](#), [Rincon 2006](#), [Ripoll 2007](#)).

HVPG has been suggested as a possible endpoint for measuring disease severity in clinical trials. There are several potential issues with this approach. First, HVPG is only effective as a monitoring tool in the patient with PH – many in earlier stages of disease will not have PH; they will have normal HVPG which won't change with treatment. Second, HVPG is invasive, expensive, and requires specialized monitoring and specially trained professionals. As a result, HVPG is only used selectively in specialized centers.

HepQuant SHUNT was developed as a global liver function test capable of monitoring hepatocellular function, total hepatic perfusion, portal inflow to the liver, and portal-systemic shunting. Similar to HVPG, HepQuant SHUNT assesses the portal circulation. In contrast to HVPG, HepQuant SHUNT accomplishes this non-invasively with high subject tolerability and lower cost. These characteristics suggest that HepQuant SHUNT could be an ideal test for measuring severity of liver disease and tracking the response of the liver to medical treatments.

In recognition of the limitations of standard lab tests, liver biopsy, and HVPG, the trans-National Institutes of Health Action Plan for Liver Disease Research and the RFA for New Technologies for Liver Disease have clearly stated the need for “non-invasive means of assessing the liver” that would “obviate the need for liver biopsy in diagnosis, staging and grading of liver diseases”

and that would “accurately reflect the stage of liver disease and can detect mild to moderate degrees of fibrosis before the onset of cirrhosis”. The HepQuant SHUNT can potentially meet these criteria.

Experience with HepQuant Tests

HepQuant™ LLC (HQ) strives to be the global leader in clinically relevant non-invasive assessment of global liver function and physiology. The HepQuant SHUNT test is a blood-based, non-invasive test well tolerated by patients, simple to administer, and test administration does not require expensive equipment or technology. Over 1600 tests have been performed in approximately 700 subjects.

This experience encompasses healthy subject controls, and patients with chronic hepatitis C, NAFLD/NASH, primary sclerosing cholangitis (PSC), hepatocellular carcinoma (HCC), polycystic liver disease, and spans the spectrum from minimal to advanced fibrosis and compensated to decompensated disease ([Everson 2007](#), [Everson 2008](#), [Everson 2009](#), [Everson 1993](#), [Shrestha 1997](#), [Everson 2012](#), [Everson 2013](#), [Helmke 2015a](#), [DeMark 1982](#), [Kern 1982](#), [Everson 1987](#), [Everson 1988](#), [Everson 1992](#), [Lee 2004](#), [Di Bisceglie 2008](#), [Helmke 2013a](#), [Helmke 2013b](#), [Helmke 2013c](#), [Helmke 2013d](#), [O'Leary 2014](#), [Helmke 2015b](#)).

Cholates

The HepQuant tests measure the clearance of cholates labeled with molecular probes (carbon-13 [¹³C], and deuterium [4D]). Cholates are naturally occurring endogenous compounds found in the human body and ¹³C and 4D are also naturally occurring non-radioactive cold stable isotopes.

Cholates labeled with stable isotopes in the amounts administered in the HepQuant tests have no known harmful effects. Because clearance of cholate from the blood is a liver specific flow-dependent function, measuring cholate clearance is a non-invasive method for assessing the severity of liver disease in intact humans.

Measuring Disease Severity

In prior studies of chronic hepatitis C, the Disease Severity Index (DSI) from the HepQuant SHUNT test correlated with ISHAK and METAVIR stages of fibrosis and predicted likelihood of cirrhosis, varices, and risk for clinical outcome. DSI has performed similarly in patients with chronic hepatitis C, NAFLD, and PSC.

Measuring Treatment Effect

Serial changes in DSI have been assessed in patients with chronic hepatitis C, during and after antiviral treatment, and in patients with PSC. There were two studies of HepQuant SHUNT for measuring impact of sustained viral response, SOLAR-1 and HALT-C. In SOLAR-1, patients were treated with ledipasvir/sofosbuvir/ribavirin, and in HALT-C, patients were treatment with peginterferon/ribavirin. HepQuant SHUNT was performed at baseline and at weeks 4, 24, 36, and 48 in SOLAR-1; and, at baseline and after approximately 2 years in HALT-C. In the PSC study, patients underwent HepQuant SHUNT tests at baseline and after 1 year.

In SOLAR-1, DSI improved significantly by week 4. The improvement was greatest in transplant recipients with necro-inflammation and non-cirrhotic stages of fibrosis (Δ DSI -4.4 $\pm$ 3.7, $p < 0.0001$) and in transplant recipients with cirrhosis (Δ DSI -1.7 $\pm$ 2.5, $p < 0.03$). DSI did not change in non-transplant patients with end-stage decompensated disease (Δ DSI 0.2 $\pm$ 2.8,

p = not significant). Standard laboratory tests, [REDACTED], and CP score failed to detect the improvement in liver function at week 4.

The results in SOLAR-1 suggest that the decrease in DSI by week 4 was likely due to improvement in the hepatic microcirculation. First, ALT declined in parallel with the clearance of HCV RNA indicating reduction in necro-inflammation. Second, platelet count increased in Lymphatic Tissue Fibrosis and Lymphatic Tissue Cirrhosis, most probably from a reduction in splenic sequestration as hepatic resistance declined and portal hypertension improved. Third, the increase in platelet count correlated with the decrease in DSI. Fourth, although improvement in hepatocyte uptake of cholate might also account for the increases in hepatic filtration rates (HFRs) and decline in DSI, there was no improvement in blood tests of hepatocyte function, such as bilirubin, albumin and INR. These findings are consistent with the interpretation that early hepatic improvement measured by drop in DSI reflects improvement in the hepatic microcirculation.

Early detection of change in function by change in DSI, and the link to changes in the hepatic microcirculation are highly relevant to the pathophysiologic changes occurring in liver disease. With successful treatment, these changes may reverse which should manifest as improved hepatic perfusion and hepatocyte uptake – events that should be detected by drop in DSI from the baseline test. If treatment has a very rapid onset of action, we could possibly detect improvement at a very early time point.

Tolerability

Over 1600 HepQuant SHUNT tests have been performed in approximately 700 patients without any untoward effects. In the GILEAD SOLAR-1 study of ledipasvir/sofosbuvir/ribavirin treatment of hepatitis C in decompensated cirrhosis or in liver transplant recipients, HepQuant SHUNT tests were performed 5 times over 48 weeks in each of 31 study participants. All 31 patients completed a survey of their experience with the HepQuant SHUNT test after a mean ($\pm$ standard deviation) of 4.5 ± 0.6 tests. Pain was rated 0.5 ± 0.8 , where 0 was no pain and 10 was severe pain. Discomfort was rated 0.3 ± 0.5 , where 0 was no discomfort and 10 was severe discomfort. Inconvenience was rated 0.4 ± 0.9 , where 0 was no interference with daily activity and 10 was complete inability to conduct usual daily activity. The recording of time commitment indicated <3 hours in 23 cases and >3 h in 8 cases.

Overall experience with the test was rated 9.5 ± 1.1 , where 0 was very negative and 10 was very positive. Willingness to undergo additional testing was rated 9.1 ± 1.8 , where 0 was definitely not willing and 10 was very willing.

Specific Aims

The objective of use of the HepQuant SHUNT test in this study is to determine whether serial changes in DSI detect a treatment effect, and to define the relationships of change in DSI (Δ DSI) to the changes in the other tests used for measuring treatment effects.

The primary aim of the HepQuant study is to compare the change in DSI between treatment arms at each time point over the time period of the study.

Additional details of the analysis will be specified in the SAP and/or a separate analysis plan.

Subjects

At qualified US sites only, subjects will also undergo evaluation using the HepQuant SHUNT test. The exclusion criteria for the HepQuant portion of the trial are identical to the overall trial, including the following:

- Subjects with extensive resection of large segments of small intestine (short gut) or severe gastroparesis
- Subjects on either a non-selective beta blocker or an ACE inhibitor or ARB who are unwilling to delay taking their normal dose the morning of their testing.
- Subjects with a known sensitivity to albumin preparations
- Subjects who are allergic to any ingredient in the formulations or components in the HepQuant SHUNT kit

Research Plan

Informed Consent

Subjects will sign an informed consent to participate in the HepQuant portion of the study.

Criteria for when an individual will stop their participation in the HepQuant study:

- Any subject with a hypersensitivity reaction to any component of the HepQuant SHUNT test kit will be withdrawn from the HepQuant SHUNT portion of the study and will not undergo any further testing with the HepQuant SHUNT Kit.
- Any subject experiencing an unanticipated SAE determined to be related to the HepQuant test or any component of the HepQuant SHUNT test kit will not undergo further testing with the HepQuant SHUNT Kit.

Criteria for when the HepQuant study will be stopped:

- The HepQuant portion of the study will be stopped entirely if two or more events meeting the definition of an Unanticipated Adverse Device Effect (812.3(s)) occur.

The overall study may continue if the HepQuant portion is stopped for this or any other reason.

Study Procedures

Screening assessments will be as outlined for the main trial and completed within the specified timeframe prior to enrollment of the subject into the clinical trial.

After enrollment, study visits for HepQuant SHUNT test will occur at designated time intervals throughout the respective clinical trial. Subjects will undergo the test at Day 1 and Week 12 of the DB Phase, then again at Week 60 of LTSE. Vital signs will be performed prior to each HepQuant SHUNT test and the test cancelled or postponed if vital signs are unstable. For example, if diastolic blood pressure is >110 mmHg the test will be canceled or postponed until the subject's blood pressure can be evaluated and brought under control. Once the blood pressure is controlled the test may be performed. AEs and SAEs will be assessed at each study visit.

Other assessments at the study visits will be defined from the visit schedule of the overall clinical trial. These assessments could include clinical evaluation, laboratory tests, [REDACTED], imaging, [REDACTED], HVPg, determination of clinical scores (e.g., [REDACTED] CP) and assessment of AEs and SAEs related to the drug under investigation in the clinical trial.

Compounds in the HepQuant SHUNT Test

The cholate testing compounds will be purchased from a qualified supplier of clinical trials grade material. [24-¹³C]cholate (¹³C-CA) and [2,2,4,4-d]cholate (d4-CA) are formulated in 1.0 meq/mL sodium bicarbonate (USP grade) to achieve concentrations of 4 mg/mL. Formulation will take place at a registered 503B outsourcing compounding pharmacy and are tested and certified to be sterile and pyrogen-free. The absolute concentrations of ¹³C- and d4-cholate are defined by liquid chromatography-mass spectrometry methods. Use of the test in this study will be reviewed by the US FDA under an Investigational Device Exemption (IDE) application. Use of the test will not begin until FDA approval of the IDE has been obtained.

HepQuant SHUNT Liver Diagnostic Kits

Test kits are shipped directly to clinical sites which function as testing centers. In brief, the HepQuant SHUNT Liver Diagnostic Kit contains:

- Sealed vial of sterile solution of 4D-CA (40 mg) in sodium bicarbonate for oral use
- Sealed vial of sterile solution of ¹³C-CA (20 mg) in sodium bicarbonate for intravenous use
- Sealed vial of 20 mL of 25% human serum albumin for intravenous use
- 6 transfer tubes and pipettes (for transport of serum to HepQuant designated lab)
- Labels
- Instructions for Use
- Test requisition form
- Supplies and labels for returning the samples for analysis

Test Administration

The HepQuant SHUNT test is performed after at least 5 hours of fasting, usually after an overnight fast, and requires venous access via a standard indwelling peripheral venous catheter, preferably placed in the antecubital fossae. 3 mL blood samples are obtained at baseline and at 5, 20, 45, 60, and 90 minutes after dosing with the cholate solutions; and ≥1 mL serum is shipped at ambient temperature to the HepQuant laboratory for analysis of cholate concentrations.

The subject may be in a bed seated upright or in a recliner chair – the subject should be seated in an upright position, or if in bed, have the head of the bed elevated by at least 30 degrees to aid gastric emptying of the orally administered dose of 4D-CA solution.

Prior to administration, the HepQuant SHUNT Liver Diagnostic Kits are kept at ambient temperature. For the oral 4D-CA dose, the full contents of the d4-CA solution are poured into a 40 mL cup and flavoring added. For the intravenous ¹³C-CA dose, 5 mL (from a total of 5.5 mL) are removed from the ¹³C-CA solution vial and mixed with 5 mL of the albumin solution (25%

w/v human serum albumin, USP grade, GRIFOLS). The ^{13}C -CA/Albumin mixture is injected intravenously over 1 minute by the person administering the test. The 4D-cholate/flavoring mixture is administered orally simultaneously over the same minute. The Instructions for Use accompanying each HepQuant SHUNT Liver Diagnostic Kit describes two acceptable methods for test administration. The Two-Arm method uses the intravenous (IV) catheter solely for blood sampling. A separate butterfly or small catheter, placed in the opposite arm, is used for injection of the IV cholate/albumin solution. The Two-Arm method is the preferred method of administration. The Single-Arm, Single-Catheter method uses the same catheter for both injection of the IV cholate/albumin and subsequent blood sampling. The Instructions for Use emphasizes adherence to a strict flushing procedure if the Single-Arm, Single-Catheter is used – to avoid carryover of the injected cholate solution into the subsequent blood samples.

If the subject were to experience an anaphylactic or hypersensitivity reaction to the compounds, administration should be stopped, and the subject should be treated in accordance with standard of care. The subject should not undergo any future HepQuant tests but may remain enrolled in the parallel drug study at the discretion of the investigator.

Test Outputs

Cholate concentrations (endogenous unlabeled CA, ^{13}C -CA, and d4-CA) will be measured from the timed serum samples (0, 5, 20, 45, 60, and 90 minutes) and concentrations of each labeled cholate as a function of time will be modeled as a spline curve in order to calculate the area under the concentration-time curve (AUC). The HepQuant SHUNT test parameters are:

- **Systemic HFR:** The intravenous clearance (Cl_{iv} , mL min^{-1}) is defined as the dose/AUC for ^{13}C -CA. The Systemic HFR is defined as the Cl_{iv} per kg of body weight and is expressed as $\text{mL min}^{-1} \text{ kg}^{-1}$.
- **Portal HFR:** The apparent oral clearance (Cl_{oral} , mL min^{-1}) is defined as the dose/AUC for d4-cholate. The Portal HFR is defined as the Cl_{oral} per kg of body weight and is also expressed as $\text{mL min}^{-1} \text{ kg}^{-1}$.
- **SHUNT:** SHUNT, the portal-systemic shunt fraction, is calculated as the ratio Systemic HFR/Portal HFR x 100%.
- **DSI:** The calculation for DSI is a proprietary formula derived from Systemic HFR and Portal HFR.
- **STAT:** The serum concentration of d4-cholate from the 60-minute blood sample correlates well with DSI ($r^2 = 0.88$) and is independently analyzed for links to disease severity and treatment effects, similar to the analyses for DSI.

Known Potential Risks

- Risks from the Test Compounds
 - Allergic reaction to cholate compounds (theoretical – none yet reported)
 - Allergic reaction to human serum albumin (HSA)

Reactions could include:

- rash
 - having a hard time breathing
 - wheezing when you breathe
 - sudden drop in blood pressure
 - swelling around the mouth, throat, or eyes
 - fast pulse
 - sweating
 - severe reactions are very rare, but a severe reaction (called anaphylaxis) can lead to profoundly low blood pressure and even death
- Risks from the Indwelling catheter
 - Pain with placement of catheter
 - Thrombosed vein
 - Hematoma
- Risk of Phlebotomy
 - Localized pain
 - Bruising
 - Occasional lightheadedness,
 - Fainting
 - Infection at the site (rare)
- Risk of Fasting
 - Dizziness
 - Headache
 - Stomach Discomfort
 - Fainting

Test Compounds

Cholates, labeled with stable (nonradioactive) isotopes, occur naturally and are not known to have any deleterious or adverse effects when given intravenously or orally in the doses used in HQ tests. The serum cholate concentrations that are achieved by either the intravenous or oral doses are similar to the serum concentrations of bile acids that occur after the ingestion of a fatty meal. Because cholates are naturally occurring with a pool size in humans of 1 to 5 g, the 20 and 40 mg doses of labeled cholates used in the HQ tests are unlikely to be harmful to a fetus.

However, the effects of these compounds on the fetus are not definitively known. In the clinical trials of new drug therapies, it is recommended that all participants use a highly effective form of birth control throughout the study, as outlined in [Section 8.1.1](#). All women of child-bearing potential will be given a urine pregnancy test at the beginning of each testing visit to ensure the

subject is not pregnant. There are no additional warnings related to pregnancy and the HepQuant SHUNT test.

The two cholates used in the HepQuant test for this study are labeled with stable (non-radioactive) forms of carbon and hydrogen that are found in nature and can be measured in blood. These forms of cholate have been used with FDA INDs (65121 and 65123) since 2002, and their use in humans has been monitored since that time. To date, the cholates used in this study have not been associated with any allergic reactions or side effects. However, they are still considered experimental and there may be unknown risks.

HSA is mixed with the ^{13}C -cholate for intravenous injection. Some individuals may have a known reaction to serum albumin and will be excluded from this study. Possible AEs from the HSA may include allergic reaction. Rare Hypersensitivity Reactions have been reported to human serum albumin preparations and include anaphylaxis, severe anaphylaxis or anaphylactoid reactions, fever, chills, rash, urticaria, pruritus, angioneurotic edema, and erythema or flushing. Individuals who are hypersensitive to albumin preparations, any ingredient in the formulation, or components of the containers should be excluded from this study.

Risk of Transmissible Diseases in Plasma-derived Preparations. Because human albumin is prepared from pooled human plasma, there is a potential to pass human viruses (e.g., hepatitis viruses, HIV) to the recipient and may carry a risk of transmitting Creutzfeldt-Jakob disease (CJD) or its variant CJD (vCJD). Donor plasma screening and specific procedures like pasteurization to eliminate or inactivate any possible causes have reduced but not entirely eliminated the risk of transmission of disease-causing agents. Risk of transmission of viral disease with plasma-derived human albumin is considered extremely remote. No causes of transmission of hepatitis B virus, HCV, or HIV have been documented following use of commercially available human albumin. There are no documented cases of CJD or vCJD transmitted through plasma-derived preparations (including plasma-derived human albumin); theoretical risk for transmission of CJD with commercially available human albumin is considered extremely remote.

However, no purification method has been shown to be totally effective in removing the risk of viral infectivity from plasma-derived preparations and because new blood-borne viruses or other disease agents may emerge which may not be removed or inactivated by current manufacturing processes, the risks of human albumin are not entirely known.

Non-selective beta blockers and ACE or ARB inhibitors could affect the blood flow to the liver, so subjects who are currently taking these medications will be asked to delay taking their normal dose the morning of their testing and until their test is completed. Delaying these medications could cause a temporary elevation in blood pressure but the risk would be minimal, similar to that of subjects that miss doses of medications in everyday life.

Test Administration

Placing the indwelling intravenous catheter will cause minor pain and discomfort. With any blood collection there is a small risk of hematoma and a very small risk of a blood clot (1 in 100) or infection (1 in 1000). Over 1600 HepQuant SHUNT tests or the prototypical dual cholate research tests have been performed on over 700 individuals and many had the test multiple times. There has never been a serious device-related AEs - the risk from the test is very small. A

questionnaire will be completed by the subject at each of the testing periods to log their experience and tolerability of HQ tests.

Data Security

HepQuant study data will be collected and entered by the site staff into an Electronic Data Capture system. Additionally, HepQuant test and analytic data will be entered by HepQuant into a secure database. HepQuant will transfer test results of the HepQuant SHUNT test to the Sponsor. The corresponding studies will be linked by de-identified study IDs.

Data stored electronically are backed up to a secure offsite location several times daily. Backup data replicated offsite is encrypted in transit and at the storage location.

Management of abnormal test results

The clinical trial protocol contains management plans for any clinically abnormal results of standard laboratory tests. The Study Coordinator, Principal Investigator, or co-Investigator will review any abnormal test results with the subject, but the HepQuant SHUNT test results will not be distributed to the subject, the treating physician, Investigators, or care providers and no treatment or management decisions will be made on the basis of these results.

Potential Scientific Problems

Use of Concomitant Medications

Non-selective beta blockers or ACE or ARB inhibitors could affect the blood flow to the liver, and therefore could affect the flow of the HepQuant SHUNT cholate test compounds into the liver as well. If the flow of blood to the liver was altered by these drugs, it could impact the SHUNT test results. Additionally, because individual subjects may take different amounts of these drugs, it is not possible to correct for the different concentrations and their impact on blood flow to the liver. As such, subjects who are currently taking either a non-selective beta blocker or an ACE or ARB inhibitor will be asked to delay taking their normal AM dose the day of their testing and until the 90-minute test is completed. Delaying these medications could cause a temporary elevation in blood pressure but the risk would be minimal, like that of subjects that delay doses of medications in everyday life. Subjects will therefore be instructed to immediately take their AM dose after the final 90-minute blood collection has been completed. Possible AEs from delaying taking ACE/ARB inhibitor or non-selective beta blockers may include minimal change in blood pressure.

Concomitant medication use could theoretically present potential interference in serum cholate measurement. The liquid chromatography-mass spectrometry technique used to measure cholate levels was validated according to FDA guidelines ([FDA 2001](#), [FDA 2018](#)) for selectivity, accuracy, precision, recovery, stability, and freedom from interferences by serum components or medications. Freedom from interference was tested on blanks and at the lower limit of quantitation for each analyte with a number of metabolites and medications including: Bilirubin, Cholesterol, Carbamazepine, Oxazepam, Diazepam, Nordiazepam, Lorazepam, Temazepam, Flunitrazepam, Nitrazepam, Clonazepam, Alprazolam, Ephedrine, Codeine, Diphenhydramine, Nortriptyline, Propoxyphene, d-Amphetamine, d-Methamphetamine, Phenylpropanolamine, Phenmetrazine, Caffeine, Phencyclidine, Imipramine, Spironolactone, Furosemide, and dl-Propranolol. There was no interference at the concentrations tested which were above those usually observed in subject serum samples.

Associated Conditions

Resection of large segments of small intestine (short gut) or severe gastroparesis could potentially affect absorption of the orally administered 4D-cholate. Therefore, subjects with these conditions will be excluded.

Number of Sites/Subjects

The HepQuant substudy will be conducted at up to 50 US sites. Subjects will have the option of enrolling into the clinical trial and the HepQuant sub study will enroll up to 48 subjects (12 subjects per group) into the HepQuant SHUNT portion of the study. As enrollment in the study is competitive among sites, up to 50 subjects may be enrolled in the HepQuant portion of the study.

Analysis of Results

Liver function evaluated by HepQuant-SHUNT will be summarized with descriptive statistics at baseline and Week 12, and at the end of LTSE visits. The major objective of this HepQuant SHUNT study is to determine whether serial changes in DSI detect a treatment effect, and to define the relationship of change in DSI to change in other measures of treatment response.

Further analysis details will be specified in the SAP and/or a separate clinical pharmacology analysis plan. For responder analyses using DSI as the endpoint, a significant treatment response in a given subject will be defined as a two point or greater decrease in DSI.

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APPENDIX C. SUMMARY OF CHANGES: PROTOCOL 747-214 VERSION 6.0 (DATED 18 DECEMBER 2023)

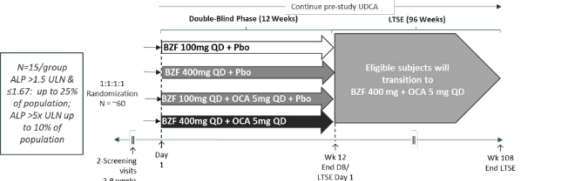
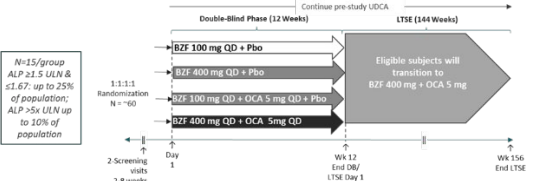
The following is a summary of key changes made to Protocol 747-214 Version 6.0:

- Updated background information of PBC and treatment landscape based on a recent literature search.
- Updated the OCA and FDC clinical program status.
- Added evidence of portal hypertension to Table 6 which lists clinical reasons for investigational product permanent discontinuation.
- Extended the total duration of the LTSE Phase from 108 weeks to 156 weeks and updated the Schedule of Study Procedures (Table 4) to add LTSE visits and assessments on Weeks 120, 132, 144 and 156 visits.
- Added an unscheduled visit column to the Schedule of Study Procedures (Table 4), which is optional and should occur as needed based on Investigator discretion; a PK sample should be collected if an unscheduled visit occurs due to a safety event.
- In the LTSE Phase subjects will receive OCA 5 mg + 400 mg BZF IR once daily dose regimen (OCA 5 mg tablet + 2 BZF 200 mg IR tablets). After interim data review of Study 747-213 DB Phase, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal. Therefore, no other dose regimen will be used in the LTSE Phase.

The text deleted from Protocol Version 5.0 is crossed out and revised text in Version 6.0 is indicated in bold font in the following table. Each revision also includes a reason or justification for the change. Section numbers refer to Version 5.0 unless otherwise stated. Sections with extensive changes that are discussed elsewhere have been summarized rather than highlighting exact changes. Minor changes including typos or editorial revisions are not listed individually in the following table.

Section	Original Text (Version 5.0, 24 Feb 2023)	Revised Text (Version 6.0, 18 Dec 2023)	Key Change Reasons/ Justification for Change
Sponsor's Approval of the Protocol	[REDACTED], MD [REDACTED], Clinical Development Intercept Pharmaceuticals, Inc.	[REDACTED], MD [REDACTED], Clinical Development Intercept Pharmaceuticals, Inc.	Change in personnel.
Study Personnel Contact Information	[REDACTED], MD, MSc [REDACTED] LabeCorp Drug Development Inc. Phone: [REDACTED] Email: [REDACTED] [REDACTED], MD, PMBA [REDACTED], Clinical Development Intercept Pharmaceuticals, Inc. (Intercept) New York, NY 10001 Mobile: [REDACTED] [REDACTED]	[REDACTED], MD, [REDACTED] Fortrea Phone: [REDACTED] Email: [REDACTED] [REDACTED], MD, PMBA [REDACTED], Clinical Development Intercept Pharmaceuticals, Inc. (Intercept) Morristown, NJ 07960 Mobile: [REDACTED] [REDACTED]	Updated contact information.
Synopsis Studied Period	Estimated date last subject completed: Aug 2024	Estimated date last subject completed: Aug 2025	Extended last subject completed date to align with the extension of the LTSE Phase.
Synopsis Additional Objectives 6.3 Additional Objectives	To assess the effects of the combination of OCA plus BZF versus BZF alone in subjects with PBC on the following: ... • Long-term Safety Extension (LTSE) Phase: Percentage of subjects at Weeks 24, 36, 48, 60, 72, 84, 96, and 108 with ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease of ≥15% from baseline until the end of the LTSE term or study termination by subject or Sponsor (DB Week 12 is the baseline for the LTSE Phase)	To assess the effects of the combination of OCA plus BZF versus BZF alone in subjects with PBC on the following: ... • Long-term Safety Extension (LTSE) Phase: Percentage of subjects at Weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156 with ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease of ≥15% from baseline until the end of the LTSE term or study termination by subject or	Updated objective to include analysis at additional LTSE Weeks 120, 132, 144, and 156 visits to align with extension of the LTSE Phase to 156 weeks.

Section	Original Text (Version 5.0, 24 Feb 2023)	Revised Text (Version 6.0, 18 Dec 2023)	Key Change Reasons/ Justification for Change
		Sponsor (DB Week 12 is the baseline for the LTSE Phase)	
Synopsis Methodology 7.1.1 Methodology	LTSE Phase (96 weeks): Subjects who continue to meet protocol requirements will transition directly to the LTSE Phase (an open-label design) upon completion of the Week 12 visit of the DB Phase. The end of the 12 week DB Phase becomes Day 1 of the LTSE Phase. All subjects transitioning into the LTSE Phase will receive treatment with OCA 5 mg once daily + BZF 400 mg once daily (Treatment D of the DB Phase). After the completion of the DB Phase, all subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits). After adopting the OCA 5 mg once daily + BZF 400 mg once daily during the LTSE Phase, subjects may later transition to the optimized to be marketed fixed dose combination (FDC) tablet, which combines OCA and BZF in a single tablet and is planned to be used in Phase 3. The transition to the optimized to be marketed FDC will occur after agreement with relevant regulatory authorities on the efficacy, safety, tolerability, and dose response data of the combination of OCA and BZF in subjects with PBC and other developmental program elements (i.e., clinical pharmacology).	LTSE Phase (144 weeks): Subjects who continue to meet protocol requirements will transition directly to the LTSE Phase (an open-label design) upon completion of the Week 12 visit of the DB Phase. The end of the 12 week DB Phase becomes Day 1 of the LTSE Phase. All subjects transitioning into the LTSE Phase will receive treatment with OCA 5 mg once daily + BZF 400 mg once daily (Treatment D of the DB Phase). Subjects are encouraged to take investigational product each day at the same time (AM dosing for the rest of the study is preferred to align with all study visits).	Extended LTSE Phase to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites. After Interim data review of the 747-213 DB period, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal and will be continued through the open-label phase of the LTSE Phase. The FDC tablet will not be used in this study.

Section	Original Text (Version 5.0, 24 Feb 2023)	Revised Text (Version 6.0, 18 Dec 2023)	Key Change Reasons/ Justification for Change
Synopsis Methodology 7.1.1, Methodology Figure 1	 Note: Subjects who transition to the LTSE Phase will receive OCA 5 mg + BZF 400 mg QD. Once the optimized-to-be marketed FDC dose is determined and agreed upon by the relevant regulatory authorities, subjects will receive the to-be marketed FDC dose.	 Note: Subjects who transition to the LTSE Phase will receive OCA 5 mg + BZF 400 mg IR QD.	Extended LTSE Phase to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites. Clarification that the IR formulation of BZF will be used. After Interim data review of the 747-213 DB period, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal and will be continued through the open-label phase of the LTSE Phase. The FDC tablet will not be used in this study.
Synopsis Diagnosis and Main Criteria for Inclusion 8.1.1 Subject Inclusion Criteria	5. Contraception: Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥ 1 highly effective method of contraception during the study and for 30 days after the end of treatment. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from	5. Contraception: Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use ≥ 1 highly effective method of contraception during the study and for 30 days after the end of treatment. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group (CTFG) guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception	Removed repetitive text stating that the methods of contraception described are highly effective.

Section	Original Text (Version 5.0, 24 Feb 2023)	Revised Text (Version 6.0, 18 Dec 2023)	Key Change Reasons/ Justification for Change
	exposure to investigational medicinal products. Highly effective methods of contraception are as follows:	methods avoid the potential embryofetal risks from exposure to investigational medicinal products.	
Synopsis Key Exclusion Criteria 8.1.2. Subject Exclusion Criteria	3. History or presence of any of the following decompensating events: ... - Clinical evidence of decompensated liver disease or obvious portal hypertension ... - Biochemical evidence of hepatic impairment, decompensation, or injury including at least one of the following:	3. History or presence of any of the following decompensating events: ... - Clinical evidence of decompensated liver disease or portal hypertension ... - Biochemical evidence of hepatic impairment, hepatic decompensation, or injury including at least one of the following:	Clarified hepatic decompensation language.
Synopsis Investigational Products, Dosage, and Mode of Administration 11.2.2. Long-Term Safety Extension Phase	• FDC (optimized, to be marketed dose) Subjects on LTSE may later transition to the optimized to be marketed FDC dose, when available, after agreement with the relevant regulatory authorities. The FDC investigational product (optimized to be marketed dose) will be dispensed in a bottle. Each subject should take 1 tablet daily from the FDC bottle.	<i>Deletion</i>	After Interim data review of the 747-213 DB period, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal and will be continued through the open-label phase of the LTSE Phase. The FDC tablet will not be used in this study.
Synopsis Duration of Treatment 7.1.3 Study Duration	The total duration of the study per subject will be a minimum of approximately 110 weeks and a maximum of approximately 116 weeks, including a Screening Phase (a minimum of 2 weeks and up to 8 weeks), a DB Phase of 12 weeks, and an LTSE Phase of 96 weeks. Subjects who continue to meet protocol	The total duration of the study per subject will be a DB duration of 12 weeks and LTSE up to 144 weeks. Subjects who continue to meet protocol requirements will transition directly into the LTSE Phase once they complete the 12-week DB Phase.	Updated the description of the total duration of the study based on the extended LTSE Phase.

Section	Original Text (Version 5.0, 24 Feb 2023)	Revised Text (Version 6.0, 18 Dec 2023)	Key Change Reasons/ Justification for Change
	requirements will transition directly into the LTSE Phase once they complete the 12-week DB Phase.		
Synopsis Primary Efficacy Analyses in Double-Blind Phase 16.4 Secondary and Additional Efficacy Analyses	• Normalization rates at Week 12 of GGT, ALT, AST, total and conjugated bilirubin, and a lipid panel	• Normalization rates at Week 12 of GGT, ALT, AST, ALP, total and conjugated bilirubin, and a lipid panel	Updated to align with SAP and ensure inclusion of ALP.
5.1 Overview of Primary Biliary Cholangitis, Obeticholic Acid, and Bezafibrate	Primary biliary cholangitis (PBC) is a chronic, autoimmune disease characterized by cholestasis with progressive impairment of bile flow resulting in increased and potentially toxic hepatocellular bile acid concentrations. Such hepatocellular injury results in a local inflammatory response and is signaled early on by the secretion of alkaline phosphatase (ALP). The disease frequently progresses to hepatic stiffness and eventual cirrhosis, hepatic decompensation and death (Hirschfield 2013). Subjects with advanced PBC disease are also predisposed to hepatocellular carcinoma (Kuiper 2010). PBC is rare, with a reported prevalence in the US of 40.2/100,000 (Kim 2000) and more than 200 cases per million in the United Kingdom (UK) (Blachier 2013). PBC disproportionately affects women versus men approximately 10:1 and is typically diagnosed in subjects between 40 years to 60 years of age. Recent data from the large UK PBC Group have shown that those who are young at onset (diagnosed before 50 years of age) or male have a worse prognosis (Carbone 2013). While the cause of the disease is unclear, genetic predispositions have been described	Primary biliary cholangitis (PBC) is a rare, autoimmune, cholestatic liver disease, predominantly affecting women over 40 years of age (EASL 2017, Lindor 2019). It is estimated that the prevalence of PBC is 1 in 1000 women over the age of 40 years with up to 100,000 patients diagnosed with PBC in the United States (US); less than 10% of patients with PBC are male (EASL 2017). The natural history of the disease is well understood and characterized by progressive destruction of intrahepatic bile ducts resulting in chronic cholestasis, portal inflammation, and fibrosis that can lead to cirrhosis and ultimately liver failure (Murillo Perez 2020; Selmi 2011). The most common presenting symptoms of PBC are pruritus and fatigue. The diagnosis of PBC can be met with at least 2 of the following criteria: 1) biochemical evidence of cholestasis with elevation of serum ALP; 2) presence of anti-mitochondrial autoantibodies (AMA), or other PBC specific autoantibodies; or 3) histological evidence of nonsuppurative destructive	Updated background information of PBC and treatment landscape based on a more recent literature search.

Section	Original Text (Version 5.0, 24 Feb 2023)	Revised Text (Version 6.0, 18 Dec 2023)	Key Change Reasons/ Justification for Change
	(Mells 2011, Hirschfield 2009). The disease may be triggered by a response to several factors, such as infection or chemicals, followed by an autoimmune response (Pratt 2005). The most common early symptoms of PBC are pruritus and fatigue. The severity of cholestatic pruritus is not related to the prognosis or severity of the disease (Mells 2013, Beuers 2014). Pruritus frequently subsides spontaneously when cirrhosis and hepatic decompensation develop, suggesting the pruritogen is synthesized in the liver (Jones 1999). Neither the exact pruritogen nor the underlying mechanisms for the cause of cholestatic pruritus have been completely elucidated. Biochemically, PBC is characterized by increases in ALP and gamma glutamyl transferase (GGT) enzymes with or without elevations of hepatocellular transaminases and bilirubin (Lindor 2009a, Heathcote 2000). Elevations of ALP are commonly used as the biochemical endpoint for diagnosis (Lindor 2009, EASL 2017). In addition, ALP alone or with other biomarkers, such as bilirubin, is often used to assess a subject's PBC, test the efficacy of novel therapies in clinical studies, and gauge the risk of long-term adverse clinical outcomes in subjects with PBC (Carbone 2016, Lammers 2014). ALP and total bilirubin levels have also been shown to correlate with disease progression; ALP assessed over the first year with or without therapy is highly predictive of long-term clinical outcomes, such as transplant-free survival (Meaney 2011, Beuers 2011, Carbone 2013, Lammers 2013). Historically, the approved drug therapy for PBC was the bile acid ursodeoxycholic acid (UDCA), a physiological constituent of human bile (Lindor	cholangitis and destruction of interlobular bile ducts (Lindor 2019). The treatment goal for patients with PBC is to improve transplant-free survival. Historically, ALP and bilirubin levels have been the primary biochemical markers used by clinicians to determine the risk of progression and to evaluate response to treatment (Kowdley 2022, Murillo Perez 2020, Corpechot 2011, Lammers 2014). Recent data suggest that optimal survival benefit is realized when normalization of either ALP (<ULN) or total bilirubin (<0.6x ULN) are achieved (Murillo Perez 2020). High GGT levels have also been associated with increased risk of mortality and liver transplant, supporting the role of GGT as an additional prognostic biomarker of PBC (Gerussi 2021). AST and ALT may also provide additional prognostic information as the AST/ALT ratio is associated with disease progression, particularly in patients with advanced histologic stages III to IV (Gatselis 2020, Trivedi 2014). The relative importance of each of these plasma biomarkers remains a key focus of clinical research. It is also increasingly clear that the amount of time an individual spends with abnormal biochemistries is predictive of increased risk (Kowdley 2023, Soret 2021). Ursodeoxycholic acid (UDCA), the only approved first-line treatment for PBC, has been demonstrated to provide an insufficient response in many patients. The addition of obeticholic acid (OCA) as a second agent has been shown to improve biochemical responses in ALP and bilirubin for up to 6 years through long-term, open-label extensions of clinical studies. However, despite substantial reductions in ALP	

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	2009b). While UDCA therapy had a marked effect on the treatment of PBC, up to 50% of subjects showed a suboptimal response or no response to UDCA (Corpechot 2008, Kumagi 2010). Such subjects were at significantly increased risk of a poor clinical outcome due to PBC disease progression. Obeticholic acid (OCA), a farnesoid X receptor (FXR) agonist and modified bile acid derived from the primary human bile acid chenodeoxycholic acid (CDCA), was developed for the treatment of PBC and to provide subjects who have an inadequate response to or poor tolerance of UDCA, a novel treatment option that was safe and effective (Pellicciari 2002). OCA is approved under the tradename Ocaliva® by the Food and Drug Administration (FDA), European Medicines Agency (EMA; conditional approval), Health Canada, and other regulatory agencies for the treatment of PBC in combination with UDCA in adults with inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. The indication was approved under accelerated/conditional approval based on a reduction in ALP. The Core Company Data Sheet (CCDS) was updated on 01 June 2021 and states that OCA is now contraindicated in patients with PBC with decompensated cirrhosis or a prior decompensation event, or complete biliary obstruction. Bezafibrate (BZF), a pan-peroxisome proliferator-activated receptor (PPAR) [α, δ, γ] agonist, was originally developed for treatment of hyperlipidemia and used for the prevention of cardiovascular disease. BZF also decreases serum hepatobiliary enzyme activity in individuals with and without cardiovascular disease and thus has been identified as a potential anticholestatic agent for the treatment of PBC with an	and bilirubin, many patients with PBC administered UDCA and OCA remain at an elevated risk for disease progression. Other treatment options for PBC include the off-label use of fibrates. Bezafibrate (BZF) has not been approved for any indication in the US or any country for the treatment of patients with PBC, and a full clinical developmental program with BZF or any fibrate for the treatment of PBC has not been completed. However, fibrate treatment (including treatment with BZF) has been incorporated in various PBC treatment guidelines as an adjunctive therapy to UDCA for patients with PBC with an inadequate response to UDCA (Lindor 2022, EASL 2017). In a large retrospective cohort study of treatment effects in patients with PBC with an incomplete response to UDCA, the addition of BZF (a pan-peroxisome proliferator-activated receptor [PPAR] agonist) was associated with improved long-term liver transplantation-free survival (Tanaka 2021). Additionally, 2 clinical proof-of-concept studies have demonstrated that the combination of OCA and BZF had a strong, additive, beneficial effect on biomarkers of cholestasis in patients who had a sub-optimal response to second line therapies (Smets 2021, Soret 2021). Taken together, these studies suggest that OCA in combination with BZF has the potential for synergistic activity between farnesoid X receptor (FXR) and PPAR agonists. To address the urgent unmet need for effective PBC therapies, the Sponsor has initiated a development program with combination OCA and BZF to maximize the proportion of patients	

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	inadequate response to UDCA. The mechanism by which BZF improves cholestasis and modifies the immune response in subjects with PBC is incompletely understood (Yin 2015); however, Honda 2013 demonstrated that BZF inhibits hepatic synthesis and the uptake of bile acids, enhances bile acid detoxification, and stimulates canalicular MDR3, MDR1, and MRP2 activities via PPAR activation (Honda 2019). A meta-analysis of studies evaluating BZF in combination with UDCA in PBC subjects demonstrated a clear improvement in several liver-related parameters within 1 month of treatment (Yin 2015). Significant changes were noted in GGT, ALP, immunoglobulin (Ig)M and the Mayo Risk Score, which is used as an indicator of PBC severity. Furthermore, a retrospective analysis in 118 Japanese subjects who had received UDCA monotherapy for at least 1 year followed by combination therapy with UDCA + BZF for at least 1 year demonstrated improved GLOBE and UK-PBC scores and long-term prognosis of the PBC subjects (Honda 2019). European Association for the Study of the Liver (EASL) guidelines suggest that the off-label use of BZF may be an appropriate second-line therapy in subjects with an inadequate response to UDCA (EASL 2017). In a 24-month, double-blind, placebo-controlled study in subjects who had an inadequate response to UDCA, subjects assigned to receive BZF were given daily doses of 400 mg BZF with UDCA. The subjects taking BZF/UDCA had a significantly higher rate of complete biochemical response (31%) than subjects taking placebo/UDCA (0%) (Corpechot 2018). Additionally, a recent study demonstrated that UDCA and BZF combination therapy was more effective than UDCA monotherapy in improving	with PBC who rapidly achieve biochemical remission with a well-tolerated oral therapy.	

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	alanine transaminase (ALT), ALP, and GGT. There was no difference between the two groups in bilirubin, AST, or albumin and none of the adverse effects differed statistically between the 2 groups (Agrawal 2019).		
5.3.2. Bezafibrate	Addition	The Sponsor has completed a rodent combination toxicology study per International Conference on Harmonisation (ICH) guidance on nonclinical safety studies (ICH M3[R2]).	Updated status of rodent combination toxicology study.
5.4.1 Obeticholic Acid	As of 26 Nov 2022, since the commencement of the development program, approximately 4566 subjects (3523 patients and 1043 healthy volunteers) have received OCA in clinical studies sponsored by Intercept and Sumitomo Pharma Co., Ltd., (Intercept's former co development partner in China, Korea, and Japan). The estimated cumulative patient exposure from marketing experience is 32,793 patient-years. ... To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double blind, Phase 2 studies (747-201 and 747-202), and 1 placebo-controlled, double blind Phase 3 study (747-301). Following the double blind phase, subjects in all 3 studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301. The efficacy and safety of OCA was also evaluated in a placebo-controlled, double-blind, Phase 3b/4 study (747-302), which was a post-marketing requirement (PMR) study in PBC. Study 747-201 (59 subjects) evaluated 2 doses of OCA (10 mg and 50 mg) given as monotherapy	As of 26 May 2023, since the commencement of the development program, approximately 4616 subjects (3549 patients and 1067 healthy volunteers) have received OCA in clinical studies sponsored by Intercept and Sumitomo Pharma Co., Ltd., (Intercept's former co development partner in China, Korea, and Japan). The estimated cumulative patient exposure from marketing experience is 37,194 patient-years. ... OCA (Ocaliva) has received marketing authorization in the US, Europe, and several other countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Per the Core Company Data Sheet (CCDS) v.4.0, Ocaliva is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event and in patients with complete biliary obstruction. In the US, per United States Prescribing Information (USPI), Ocaliva is also contraindicated in patients with compensated cirrhosis with evidence of portal hypertension.	Updated OCA exposure information. Updated and clarified status of OCA clinical development program.

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	versus placebo. Statistically significant and clinically relevant relative and absolute reductions from baseline in ALP were achieved with both doses of OCA versus placebo ($p < 0.0001$). Mean relative ALP reductions were 44.5% (OCA 10 mg) and 37.6% (OCA 50 mg) compared to an increase of 0.4% with placebo. Further, significant improvements in GGT and in conjugated bilirubin were observed with both doses compared with placebo ($p < 0.05$). OCA also resulted in decreased circulating ALT and AST levels. • Study 747-202 (165 subjects) evaluated 3 doses of OCA (10 mg, 25 mg, and 50 mg) versus placebo in subjects on a stable therapeutic dose of UDCA. Overall, the data from 747-202 were consistent with Study 747-201. Statistically significant and clinically meaningful relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p < 0.0001$). Mean ALP reductions from baseline ranged from 21% to 25% compared to 3% with placebo. Improvements were also seen in GGT and ALT levels and in conjugated bilirubin levels. • Study 747-301 (216 subjects) was a Phase 3, double-blind, placebo-controlled, parallel-group study followed by an LTSE Phase using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects reaching specific criteria for ALP and bilirubin (ALP $< 1.67 \times$ upper limit of normal [ULN] with a $\geq 15\%$ reduction and bilirubin $\leq$ ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to $< 1.67 \times$ ULN with a $\geq 15\%$ reduction from baseline and a normal bilirubin level after 12 months of therapy. The placebo group experienced a mean decrease in ALP from baseline of 5%, compared to a significant mean decrease of 39% in the 10 mg OCA dose group and 33% in the OCA	The PBC indication was approved based on a reduction in ALP. Data that supported approval of Ocaliva included 3 randomized, double-blind, placebo-controlled, multi center, international studies in subjects with PBC: • Study 747-201 was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in subjects with a proven or likely diagnosis of PBC who were suboptimally controlled. In this study, OCA doses of 10 mg and 50 mg were evaluated as monotherapies. • Study 747-202 was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in subjects with a proven or likely diagnosis of PBC who were suboptimally controlled. OCA doses of 10 mg, 25 mg, and 50 mg were evaluated as add-on therapy to UDCA, the current standard of care for PBC. • Study 747-301 was the pivotal Phase 3, 12-month, international, double-blind, placebo-controlled study in subjects with a proven or likely diagnosis of PBC who were suboptimally controlled. In this study, OCA doses evaluated were 10 mg or a titration approach (i.e., 5 mg for the initial 6 months, with uptitration to 10 mg for the last 6 months if the subject did not meet the primary composite endpoint and had no tolerability issues). Each of these 3 studies included open-label, uncontrolled, LTSE phases to evaluate the long-term effects of OCA treatment. The LTSEs of Studies 747-201, 747-202, and 747 301 are completed. An additional, 8-week, open-label study was also supportive of Ocaliva approval; however, efficacy	

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	titration group (both OCA dose groups $p < 0.0001$ versus placebo): • The LTSE phases of both Phase 2 studies and the Phase 3 study, were completed and demonstrated the long-term safety and durable therapeutic response of OCA. Study 747-302 was a post-marketing requirement (PMR) study designed to confirm the clinical benefit of OCA treatment in subjects with PBC. The study was discontinued early due to feasibility challenges and potential futility as OCA became commercially available during the study. This resulted in an underpowered study with likely crossover bias. No treatment difference was seen between the placebo group and OCA for the primary composite endpoint that may be the result of a crossover bias (or other elements) mentioned above. Based on the updated CCDS which contraindicates OCA in patients with PBC with decompensated cirrhosis or a prior decompensation event, or complete biliary obstruction, one post-marketing study in PBC was closed (Study 747-401). • Study 747-401 evaluated the PK and safety of OCA treatment in subjects with moderate and advanced cirrhosis, a population that is now contraindicated per the United States Prescribing Information (USPI), European Union (EU) summary of product characteristics (SmPC), and CCDS. Though the data were limited, the PK findings were as expected, and no new safety findings were noted. No efficacy benefit was demonstrated, though the study was not designed for such analyses with very low number of subjects. Refer to the latest version of the OCALIVA-US Package Insert (US Label) for additional information regarding OCA safety.	data from this study was not integrated with Studies 747-201, 747-202, and 747-301 due to differences in study design and endpoints: • Study 747-205 assessed the safety, tolerability, and PD effects of OCA on HDLc metabolism in subjects with PBC on a stable dose of UDCA. As of 26 May 2023, the LTSE phase is completed. Completed postmarketing requirement studies in subjects with PBC included the following: • Study 747-302 (postmarketing requirement) was a double-blind, randomized, placebo-controlled, multicenter study designed to prospectively obtain evidence to confirm clinical benefit and further evaluate the benefit-risk profile of OCA treatment in subjects with PBC. • Study 747-401 (postmarketing requirement) was a double-blind, randomized, placebo-controlled study evaluating the PK and safety of OCA in subjects with PBC and moderate to severe hepatic impairment. Enrollment in studies 747-302 and 747-401 was paused starting in early 2020 due to the COVID 19 pandemic and data monitoring committee (DMC) recommendations. Studies 747-401 and 747-302 were terminated in July 2021 and December 2021, respectively. Of note, neither of the studies were terminated for a safety reason. OCA is also being evaluated in other indications, including biliary atresia (BA). Refer to the latest version of the Ocaliva US Package Insert (US Label) for additional information regarding OCA safety.	

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5.4.2. Bezafibrate	Although BZF is not licensed for treatment of subjects with PBC, both the AASLD and EASL guidelines for PBC mention the investigational or off-label use of fibrates for the treatment of PBC (Lindor 2009a, EASL 2017).	Although BZF is not licensed for treatment of subjects with PBC, both the AASLD and EASL guidelines for PBC mention the investigational or off-label use of fibrates for the treatment of PBC (Lindor 2022 , EASL 2017).	Updated reference.
5.5.1. Rationale for Combination Study Design	The conclusion of the authors was that combination therapy of OCA and BZF in subjects with PBC had a strong additive effect on cholestasis and improved pruritus (Smets 201).	The conclusion of the authors was that combination therapy of OCA and BZF in subjects with PBC had a strong additive effect on cholestasis and improved pruritus (Smets 2019, Smets 2020).	Added new reference.
5.6 Importance of Monitoring of Disease Progression	Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring. ... Subjects will be monitored for potential hepatic injury and/or decompensation and progression to cirrhosis (Section 7.4).	Investigators, together with the Sponsor's Medical Monitor, will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or hepatic decompensation coupled with rules-based laboratory monitoring as well as Investigator and Sponsor discretion Subjects will be monitored for potential hepatic injury and/or hepatic decompensation and progression to cirrhosis (Section 7.4).	Clarified that the decompensation referred to is hepatic decompensation.
5.7.2. Risks Table 1 Known and Potential Risks of OCA	Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dosage for that patient population; however, cases of hepatic decompensation and failure have continued to be reported in patients	Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dosage for that patient population; however, cases of hepatic decompensation and failure have continued to be	Clarification to align with current labeling.

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	with decompensated cirrhosis even when they received the recommended dosage.	reported in patients with decompensated cirrhosis even when they received the recommended dosage. Per the CCDS v.4.0, Ocaliva is contraindicated in patients with PBC with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event and in patients with complete biliary obstruction.	
7.1.2 Schedule of Study Procedures, Table 3	° Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (quantitative β -hCG) blood test must be performed at the central laboratory.	° Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory.	Clarified serum quantitative β -hCG analysis used for serum pregnancy test.
7.1.2 Schedule of Study Procedures, Table 4	<i>Added columns</i>	<i>Visit columns added for: LTSE Week 120, LTSE Week 132, LTSE Week 144, LTSE Week 156 (EOS), Unscheduled Visit</i>	Updated schedule of procedures to include Weeks 120, 132, 144, and 156 visits to align with extension of the LTSE Phase. Updated to include Weeks 120, 132, 144, and 156 visits to align with extension of the LTSE Phase. Added an unscheduled visit column to ensure an understanding of assessments that are required and/or optional.
7.1.2 Schedule of Study Procedures, Table 4	Note: Unscheduled visits should occur as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered.	<i>Deletion</i>	Replaced the note with a column to describe in more detail the assessments required at an unscheduled visit and/or optional.

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7.1.2 Schedule of Study Procedures, Table 4	¹ Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (quantitative β -hCG) blood test must be performed at the central laboratory.	¹ Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory.	Clarified serum quantitative β -hCG analysis used for serum pregnancy test.
7.1.2 Schedule of Study Procedures, Table 4	¹ Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (quantitative β -hCG) blood test must be performed at the central laboratory.	¹ Urine-based β -hCG pregnancy tests must be performed in females of childbearing potential prior to entry and at every visit. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory.	Clarified serum quantitative β -hCG analysis used for serum pregnancy test.
7.1.2 Schedule of Study Procedures, Table 4	^r ... A PK sample at pre-dose and 4 hours post-dose will be drawn at 1 LTSE visit only, which will occur at the visit following the transition to the to-be-marketed fixed-dose combination (FDC) tablet.	^r	Clarification that the IR formulation of BZF will be used. Since the subjects will not switch treatment to the single FDC tablet during the LTSE phase PK sampling is no longer required and text deleted.
7.1.2 Schedule of Study Procedures, Table 4	<i>New footnote added</i>	^s Unscheduled visits are optional and should occur as needed based on Investigator discretion; a PK sample should be collected if an unscheduled visit occurs due to a safety event	Added a footnote to describe the required PK sampling in an event of an unscheduled visit.
7.3 Planned Dosing Duration	All subjects who transition to the LTSE Phase will receive the OCA 5 mg once daily + BZF 400 mg once daily dose (same as Treatment D of the DB Phase). Subjects in LTSE Phase may later transition to the optimized to-be-marketed FDC dose, when available,	All subjects who transition to the LTSE Phase will receive the OCA 5 mg once daily + BZF 400 mg IR once daily dose (same as Treatment D of the DB Phase).	Clarification that the IR formulation of BZF will be used.

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	after agreement with the relevant regulatory authorities.		
7.4 Monitoring and Management of Potential Hepatic Injury and/or Disease Progression, 7.4.1 Signs and Symptoms of Potential Hepatic Injury or Hepatic Decompensation	In addition, AEs, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.2. <i>Similar changes made in 7.4.1</i>	In addition, AEs, signs and symptoms of potential hepatic injury or hepatic decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.2. <i>Similar changes made in 7.4.1</i>	Clarified language regarding hepatic decompensation.
7.4.3 Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events, Table 6	<i>New bullet</i>	Evidence of portal hypertension (e.g. platelet count <150,000/μL, splenomegaly, presence of varices)	Added portal hypertension as reason for investigational product permanent discontinuation.
7.6.2. LTSE Phase	Subjects who continue to meet protocol requirements will transition to the LTSE Phase (an open-label design) upon completion of the DB Phase. During the LTSE Phase, all subjects will be maintained (Treatment D subjects already on transition dose) or transitioned to OCA 5 mg + 400 mg BZF once daily. Once the optimized to-be-marketed FDC dose is determined and agreed by the relevant regulatory authorities, subjects will receive the to-be-marketed FDC dose. Subjects who are transitioned to the OCA 5 mg + 400 mg BZF once daily dose (from BZF monotherapy or OCA 5 mg + 100 mg BZF) will be monitored with safety labs (liver biochemistries and CK levels) at 4	Subjects who continue to meet protocol requirements will transition to the LTSE Phase (an open-label design) upon completion of the DB Phase. During the LTSE Phase, all subjects will be maintained (Treatment D subjects already on transition dose) or transitioned to OCA 5 mg + 400 mg BZF IR once daily. Subjects who are transitioned to the OCA 5 mg + 400 mg BZF IR once daily dose (from BZF monotherapy or OCA 5 mg + 100 mg BZF IR) will be monitored with safety labs (liver biochemistries and CK levels) at 4 weeks after the transition, and if not significantly changed, then every 4 weeks until 12 weeks after the transition, at which point safety	Clarification that the IR formulation of BZF will be used. After Interim data review of the 747-213 DB period, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal and will be continued through the open-label phase of the LTSE Phase. The FDC

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	weeks after the transition, and if not significantly changed, then every 4 weeks until 12 weeks after the transition, at which point safety labs will be done every 3 months (unless there are significant changes in the labs which would be handled per protocol, refer to Section 7.4). Subjects who were on the OCA 5 mg + 400 mg BZF once daily dose during the DB-period, will not warrant additional safety labs.	labs will be done every 3 months (unless there are significant changes in the labs which would be handled per protocol, refer to Section 7.4). Subjects who were on the OCA 5 mg + 400 mg BZF IR once daily dose during the DB-phase, will not warrant additional safety labs.	tablet will not be used in this study.
9.1. Investigational Products Treatment Regimen	• FDC (optimized to be marketed dose)	<i>Deletion</i>	After Interim data review of the 747-213 DB period, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal and will be continued through the open-label phase of the LTSE Phase. The FDC tablet will not be used in this study.
9.7.2.1. Screening Visit 1	• Perform a urine-based beta human chorionic gonadotropin (β -hCG) pregnancy test for females of childbearing potential. If positive, a confirmatory serum pregnancy (quantitative β -hCG) blood test must be performed at the central laboratory.	• Perform a urine-based beta human chorionic gonadotropin (β -hCG) pregnancy test for females of childbearing potential. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory.	Clarified serum quantitative β -hCG analysis used for serum pregnancy test
9.7.4. Day 1 Procedures	• Perform a urine-based β -hCG pregnancy test for females of childbearing potential. If positive, a confirmatory serum pregnancy (quantitative β -hCG) blood test must be performed at the central laboratory.	• Perform a urine-based β -hCG pregnancy test for females of childbearing potential. If positive, a confirmatory serum pregnancy (serum quantitative β -hCG) blood test must be performed at the central laboratory.	Clarified serum quantitative β -hCG analysis used for serum pregnancy test
9.7.7. Unscheduled/Safety Visit	The Investigator may schedule an Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted.	The Investigator may schedule an Unscheduled/Safety Visit at any time if clinically warranted based on Investigator discretion. A PK sample should be collected if an unscheduled visit	Clarified a PK sample should be collected in an

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	As appropriate, the Medical Monitor should be contacted.	occurs due to a safety event. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. As appropriate, the Medical Monitor should be contacted.	event of an unscheduled visit.
9.7.8. LTSE Phase	Once the optimized to be marketed FDC dose is determined and agreed upon by the relevant regulatory authorities, subjects will receive the to be marketed FDC dose.	<i>Deletion</i>	After Interim data review of the 747-213 DB period, the Sponsor has determined that the OCA 5 mg + 400 mg BZF IR once daily dose regimen is ideal and will be continued through the open-label phase of the LTSE Phase. The FDC tablet will not be used in this study.
9.7.8.5. Weeks 36, 60, 84, 108, and 132	9.7.7.5. Weeks 36, 60, and 84 • [REDACTED]. No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.	9.7.7.5. Weeks 36, 60, 84, 108, and 132 • [REDACTED]. No alcohol consumption prior to study visit. Record the investigational product last dose (from the day prior) in the eCRF.	Updated LTSE to align with extension of the LTSE Phase to 156 weeks.
9.7.8.6. Weeks 48, 72, 96, 120, and 144	9.7.7.6. Weeks 48, 72, and 96	9.7.7.6. Weeks 48, 72, 96, 120, and 144	Updated LTSE to align with extension of the LTSE Phase to 156 weeks.
9.7.8.7. LTSE Week 156 (EOS Visit)	9.7.7.7. LTSE Week 108 (EOS Visit) The following procedures will be performed at the LTSE Week 108 /EOS Visit:	9.7.7.7. LTSE Week 156 (EOS Visit) The following procedures will be performed at the LTSE Week 156 /EOS Visit:	Updated LTSE EOS visit to align with extension of the LTSE Period to 156 weeks.

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10.2. COVID-19 Vaccine	COVID-19 vaccination (with vaccines approved for emergency use in the country where you practice) is allowable for participants enrolled in the Intercept-sponsored PBC and NASH clinical trials.	COVID-19 vaccination (with vaccines approved for emergency use in the country where you practice) is allowable for participants enrolled in this trial.	Clarified details.
11.1.3. Fixed Dose Combination	The investigational product for the FDC tablets will be supplied as white, oval, film coated tablets. The FDC tablet combines OCA and BZF in a single tablet. The dose level of the active ingredients, BZF and OCA, in the FDC tablet will be determined based on agreement with regulatory authorities. The FDC tablets are 9 mm by 19 mm oval tablets debossed with "INT" on 1 side and "3547" on the other side. Each FDC tablet contains [REDACTED] as a release controlling agent along with the following inactive ingredients: [REDACTED]. The FDC will be provided as tablets for oral administration in high density polyethylene bottles with heat induction seals and child-resistant closures, containing 30 tablets. All FDC investigational products will be manufactured according to Good Manufacturing Practices.	<i>Deleted section</i>	Removed text describing the single FDC tablet since the FDC tablet will not be used in this study.
11.2.1 Double-Blind Period	The OCA and BZF investigational product will be dispensed in dosing kits that contain 1 bottle of OCA or placebo and weekly blister wallets that contain the active BZF dose (100 mg IR or 400 mg SR) or placebo.	The OCA and BZF investigational product will be dispensed for oral administration in dosing kits that contain 1 bottle of OCA or placebo and weekly blister wallets that contain the active BZF dose (100 mg IR or 400 mg SR) or placebo.	Clarified investigational product dispensation language.
11.2.2. Long-Term Safety Extension Period	Subjects may transition to an LTSE period of the study after the DB treatment period . During the LTSE phase, subjects will receive treatment with the OCA 5 mg and BZF 400 mg IR (Treatment D of the DB Phase) for daily administration. The OCA and BZF investigational product will be dispensed in	Subjects may transition to an LTSE phase of the study after the DB treatment period . During the LTSE phase, subjects will receive treatment with the OCA 5 mg and BZF 400 mg IR (Treatment D of the DB Phase) for daily administration. The dosing kits used in the LTSE Phase of the study will be	Clarified that the dosing kits used in the DB phase will be used in the LTSE phase and will be open-label.

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	dosing kits that contain 1 bottle of OCA 5 mg and weekly blister wallets that contain the BZF 400 mg IR dose. Each subject should take 3 tablets daily, 1 tablet from the OCA bottle and 2 tablets from the weekly BZF blister wallet, during the LTSE Phase.	provided in a similar manner to those used in the DB Phase of the study. The OCA and BZF investigational product will be dispensed in dosing kits that contain 1 bottle of OCA 5 mg and weekly blister wallets that contain the BZF 400 mg IR dose. Dosing kits will be open labeled that include the OCA 5 mg and BZF 400 mg IR dose information. Kits will be dispensed to the subject according to the visit schedule in Table 4 to provide sufficient tablets for daily dosing until the next time investigational product/study medication is dispensed. Each subject should take 3 tablets daily, 1 tablet from the OCA bottle and 2 tablets from the weekly BZF blister wallet, during the LTSE Phase.	
			Clarified details.
14.1.2. LTSE PK Sampling	• A PK sample at pre-dose and 4 hours post-dose will be drawn at 1 LTSE visit only, which will occur at the visit following the transition to the to-be-marketed fixed dose combination (FDC) tablet.	<i>Deletion</i>	Since the subjects will not switch treatments to the single FDC tablet during the LTSE phase PK sampling is no longer required.
			Clarified wording to reflect the different bile acids assay methods.
15.2.4. Child-Pugh Classification	Scores will be calculated by the Sponsor and recorded on the eCRF.	Scores will be recorded on the eCRF.	Clarified details.
15.2.8 Laboratory Assessments	If a urine pregnancy test is positive, a serum pregnancy test (quantitative β -hCG) must be performed to confirm the result.	If a urine pregnancy test is positive, a serum pregnancy test (serum quantitative β -hCG) must be performed to confirm the result.	Clarified serum quantitative β -hCG analysis used for serum pregnancy test.