Clinical Study Protocol 747-213

OBETICHOLIC ACID (OCA)

A Phase 2, Double-Blind, Randomized, Parallel Group Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid Administered in Combination with Bezafibrate in Subjects with Primary Biliary Cholangitis Who Had an Inadequate Response or Who Were Unable to Tolerate Ursodeoxycholic Acid

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Sponsor

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

[redacted]

Electronically signed by: [redacted]
Reason: I have reviewed this document
Date: Oct 10, 2024 21:33 GMT+2

10-Oct-2024

[redacted] MD
[redacted], 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 747-213. 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 747-213 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

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Products:

Obeticholic acid, bezafibrate, and matching placebo

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; INT-747
Bezafibrate (BZF)

Title of Study:

A Phase 2, Double-Blind, Randomized, Parallel Group Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid Administered in Combination with Bezafibrate in Subjects with Primary Biliary Cholangitis Who Had an Inadequate Response or Who Were Unable to Tolerate Ursodeoxycholic Acid

Short Title of Study:

A Phase 2 Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid Administered in Combination with Bezafibrate in Subjects with Primary Biliary Cholangitis

Investigators and/or Study Center(s):

Approximately 55-85 investigational sites, globally

Studied Period:	**Phase of Development:**
Estimated date first subject enrolled: Nov 2019 Estimated date last subject completed: Oct 2025	Phase 2

Objectives:

Primary Objective:

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)

Secondary Objectives:

To assess the effects of the combination of OCA and BZF in comparison to 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 a lipid panel
- Biomarkers of bile acid synthesis and homeostasis, including 7α-hydroxy-4-cholesten-3-one (C4) and bile acids
- Safety and tolerability

Additional Objectives:

[redacted]

[redacted]

Methodology:

This Phase 2, proof-of-concept, randomized, double-blind, parallel-group study will evaluate the efficacy, safety, and tolerability of OCA (5 mg and 10 mg) administered in combination with 2 different BZF doses (200 mg and 400 mg) or BZF alone (at two doses, 200 mg and 400 mg) in up to 72 subjects with PBC over at least 12 weeks.

Protocol Version 2 and 3 Overview of Differences: Protocol Version 2 had a 3-arm design (Group 1, OCA 5 mg to 10 mg; Group 2, OCA 5 mg to 10 mg + BZF 200 mg immediate release [IR]; Group 3, OCA 5 mg to 10 mg + BZF 400 mg sustained release [SR]), whereas Protocol Version 3 onwards has a 4-arm design: Group 1 (Treatment A: BZF 200 mg IR); Group 2 (Treatment B: BZF 400 mg SR); Group 3 (Treatment C: OCA 5 mg to 10 mg + BZF 200 mg IR); and Group 4 (Treatment D: OCA 5 mg to 10 mg + BZF 400 mg SR). Subjects enrolled under Protocol Version 2 will remain on the initial study arm/treatment regimen (one of 3 treatment arms) throughout the double-blind (DB), DB Follow-Up, and LTSE periods while completing the visits and assessments described under the current protocol approved at the site. Upon completion of Visit 10 of the DB Follow-up period, subjects enrolled under Protocol Version 2 will transition to the LTSE period.

Screening Period (2 weeks and up to 8 weeks): Subjects will be screened for a period of 2 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 Treatment Period (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 200 mg IR once daily [QD]), Treatment B (BZF 400 mg SR tablet QD), Treatment C (OCA 5 mg→10 mg QD + BZF 200 mg IR QD), or Treatment D (OCA 5 mg→10 mg QD + BZF 400 mg SR QD).

Subjects who are randomized to combination groups will receive OCA 5 mg QD from Day 1 to the day before the Week 4 Visit, followed by OCA 10 mg QD from the Week 4 Visit through the end of the study. To preserve the study blind, appearance-matched placebo tablets for OCA and/or BZF will be administered to subjects in each treatment group from Day 1 to Week 12 as shown in the study design diagrams for the DB and LTSE treatment periods. Subjects will be instructed to begin dosing on Day 1 and to take investigational product at approximately the same time each day (morning dosing for the entire 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 the study. At study visits, all doses of investigational product will be administered at the clinic. Subjects are instructed to take investigational product with a meal onsite after all procedures have been completed or may take at home if dizziness is a concern, following a fast of at least 8 hours before dosing. A low-fat meal or meal replacement drink will be given with investigational product administration at visits with serial PK collections.

Subjects will be maintained on the DB dose and will transition to the DB Follow-Up Period on the same dose. All subjects will be held in the DB Follow-Up Period until the last subject completes Week 12 of the DB Period.

Please refer to Appendix A for a description of treatment arms and study design for subjects who were randomized under Protocol Version 2.

Randomization will be stratified by:

- Total bilirubin level (≤0.7x or >0.7x upper limit of normal [ULN] but <2x ULN)

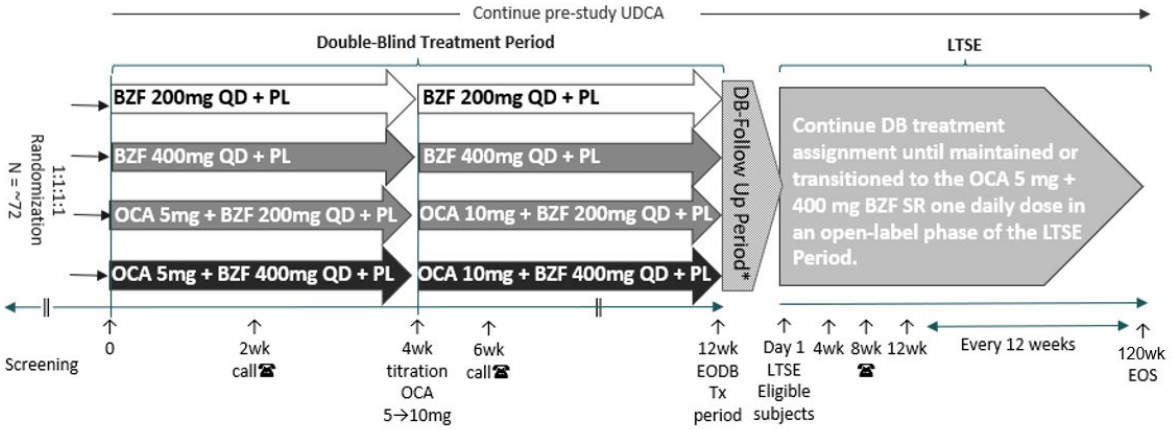
- ALP ≥1.5x ULN but ≤1.67x ULN (not more than 25% of subjects enrolled)
- ALP >1.67x ULN (remaining subjects enrolled)

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

After the Day 1 Visit, subsequent clinic visits during the DB Period will occur at approximately Weeks 4, 8, and 12 (efficacy, safety, tolerability, and PK will be assessed) and then every 12 weeks for the assessment of efficacy, safety, and tolerability. PK will not be assessed after Week 12. Subjects will also be contacted by telephone at Weeks 2 and 6 (± 5 days) to assess for occurrence of any adverse events (AEs), changes to concomitant medications and/or new medications that have been initiated, and medical/surgical procedures, and to verify that the subject is dosing as directed. During the DB Period, an interim analysis will be performed when at least 40 subjects have completed the Week 12 visit.

Long-Term Safety Extension (LTSE) Period (up to 120 Weeks): All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE. All site staff will maintain study blind until the study is moved to the open-label phase of the LTSE Period. Safety and laboratory assessments will be evaluated at clinic visits once every 12 weeks and up to Week 120.

Study Design Diagram of the Double-Blind/Follow-Up and LTSE Treatment Periods



BZF = bezafibrate; DB = double-blind; EODB = end of DB; EOS = end of study/end of LTSE Period; FDC = fixed dose combination; LTSE = long-term safety extension; OCA = obeticholic acid; QD = once daily; SR = sustained release; UDCA = ursodeoxycholic acid; PL = Placebo = either OCA or BZF tablets.

Note: *DB Follow-Up Period: Subjects will move into the DB Follow-Up Period and remain in this period until the last subject finishes the DB Period.

Note: The Screening Period is 2 weeks to a maximum of 8 weeks.

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

Note: All patients will transition to LTSE Day 1 at the same time from either the DB Period (Week 12; last subject completing the DB period) or the DB Follow-Up Period (remainder of all subjects)

Number of Subjects (Planned):

Up to 72 subjects (18 per group) will be enrolled and randomized in a 1:1:1:1 ratio to 1 of 4 treatment arms (Treatments A:B:C:D).

Diagnosis and Main Criteria for Inclusion:

1. A definite or probable diagnosis of PBC (consistent with the EASL and the AASLD guidelines [Lindor 2009; 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 (≤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 ≥1.5x ULN but ≤1.67x ULN (will not exceed 25% of subjects enrolled in the study)
   - ALP >1.67x ULN (including up to 10% of subjects with ALP >5x ULN)
   - Total bilirubin >ULN but <2x 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. Highly effective methods of contraception are as follows:
   - Intrauterine device
     - intrauterine device (IUD)
     - intrauterine hormone-releasing system (IUS)
   - Bilateral tubal occlusion
   - Vasectomy (partner)
   - Combined (estrogen and progestogen containing) hormonal contraception (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 if in line with the preferred and usual lifestyle of the subject, 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 Period.
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
- Nonalcoholic steatohepatitis (NASH)
- Gilbert's Syndrome
- 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 or asymptomatic esophageal varices)
        - Ascites/hepatic hydrothorax
        - Spontaneous bacterial peritonitis
        - Hepatic encephalopathy
        - Jaundice (with total bilirubin >3 mg/dL [>51.3 µmol/L])
    - Biochemical evidence of hepatic impairment, decompensation, or injury including at least one of the following:
        - Total bilirubin >3 mg/dL (>51.3 µmol/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 Type II) or serum creatinine >1.5 mg/dL [135 µmol/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 presence of current gallbladder diseases:
    - Cholelithiasis or cholecystitis without prior cholecystectomy
    - Choledocholithiasis without documented complete stone remove (e.g., via ERCP) and cholecystectomy

- Any size symptomatic gallbladder polyp
- Gallbladder polyp >5 mm

7. History of acute or current pancreatitis
8. History of drug-induced myopathy
9. Chronic Kidney Disease (serum creatinine >1.5 mg/dL [>135 μmol/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 or >470 milliseconds for females
13. Severe pruritus, as defined in the full protocol, 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. If female, known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
16. 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
17. 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 or lipid-lowering agents, budesonide and other systemic corticosteroids, monoamine oxidase inhibitors (MAOIs), and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, and nitrofurantoin)
18. 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
19. Participation in a study of another investigational medicine or device within 30 days before Screening
20. Treatment with commercially available OCA or other farnesoid X receptor agonists, or participation in a previous study involving OCA within 3 months before Screening
21. Unable to tolerate BZF, other fibrates, known photoallergic or phototoxic reactions to BZF or other fibrates, treatment with commercially available fibrates, or participation in a previous study involving fibrates or peroxisome proliferator-activated receptor (PPAR)-agonists within 3 months before Screening
22. 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).

23. 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
24. Blood or plasma donation within 30 days before Day 1
25. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
26. A CK value at Screening ≥5x ULN or any abnormal laboratory value that is considered CS in the opinion of the Investigator and Sponsor (at either Screening visit)
27. 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 (including total cholesterol above >10 mmol/l)

Investigational Products, Dosage, and Mode of Administration:

Tablets must be swallowed whole and not be chewed and must be taken with food and water (ad libitum) throughout the study period. Specific instructions for dosage will be provided in the protocol for PK assessment days.

- OCA 5 mg placebo tablet, QD
- OCA 10 mg placebo tablet, QD
- OCA 5 mg tablet, QD
- OCA 10 mg tablet, QD
- 200 mg BZF IR tablet, QD (BZF 200 mg QD)
- 200 mg BZF IR placebo tablet, 200 mg, QD
- 400 mg BZF SR tablet, QD (BZF 400 mg QD)
- 400 mg BZF SR placebo tablet, 400 mg, QD

DB Period: OCA and BZF investigational products 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 (200 mg IR or 400 mg SR) or placebo. Each subject should take 3 tablets daily, one tablet from the OCA bottle and 2 tablets from the weekly BZF blister wallet.

LTSE Period: Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period. In the open-label phase of the LTSE Period, OCA 5 mg + BZF 400 mg SR investigational products will be dispensed in the same manner in dosing kits that contain 1 bottle of OCA 5 mg and weekly blister wallets that contain the BZF 400 mg SR dose as previously supplied during the DB period. Each subject should continue to take 3 tablets daily, one tablet from the OCA 5 mg bottle and 2 tablets (1 tablet BZF 400 mg SR, 1 tablet Placebo 200 mg IR) from the weekly BZF 400 mg SR blister wallet.

Duration of Treatment:

The duration of treatment per subject will be a minimum of approximately 108 weeks, which includes a 12-week DB Period, followed by 120 weeks of treatment during the LTSE Period. Subjects will remain in the DB Follow-Up Period until the last subject enrolled reaches Week 12 at which point all subjects will transition to

the LTSE Period. The maximum length of time that a subject will be in the study will depend on the length of the enrolment period.

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 Intent-to-Treat (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 BZF and/or OCA during the LTSE Period.

Primary Efficacy Analyses in Double-Blind Period:

Analysis on Primary Efficacy Endpoint:

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

The primary efficacy endpoint is the change in ALP from baseline to Week 12 in the DB Period. For the primary efficacy analysis, the subjects with baseline and at least one post-baseline ALP will be included in the analysis.

[redacted]

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 endpoints include:

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

The additional efficacy endpoints include:

- Percent change from baseline of ALP at Week 12
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

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

[redacted]

Safety Analyses in Double-Blind Period:

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

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.

LTSE Analyses:

Similar analyses to those described for the DB Period will be conducted for the LTSE Period, using the DB baseline value (with the exception of PK, which will not be performed during the LTSE Period). Analyses based on the DB baseline will be performed using randomized treatment groups in the DB Period.

Interim Analysis:

There will be a planned interim analysis performed when at least 40 subjects complete the Week 12 visit in accordance with the statistical analysis plan (SAP) and data monitoring committee (DMC) Charter. The primary endpoint for this planned interim analysis will be the change from baseline in ALP at Week 12. The SAP will specify the methods for the interim analysis as well as additional details on the conductance. The interim analysis will be conducted by a Sponsor sub-team that will not be part of the study level activities. The data access plan

(DAP) will specify the make-up of the Sponsor sub-team and the appropriate data fire-walls to ensure data-integrity. The DMC will review the interim criterion for safety data and other relevant information to determine whether to continue the study.

The findings of the interim analysis will be presented to both the DMC and a Sponsor sub-team. After the interim analysis is completed, the Sponsor sub-team will review safety, efficacy, and PK data for the purpose of selecting a fixed-dose combination for a future marketed product and for regulatory interaction. With the exception of a small Sponsor sub-team who will know the results of the interim analysis, blinding of all operational site staff and the Sponsor will be maintained until the database has been locked for the DB Period. The Sponsor sub-team will be excluded from study conductance and appropriate firewalls will be established for the remainder of the DB Period (as described in the DAP). When all subjects have completed the DB Period, the study will convert to an LTSE. Details of the unblinding and data access plan will be provided in separate documents.

The efficacy measures for the interim analysis include:

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

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

Those endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.

Additional Rolling Interim Analysis

The Sponsor will have the option to perform an additional unblinded rolling analysis of efficacy, PK, and safety data throughout the DB Period. Details of the unblinding and DAP, including Sponsor staff that will be unblinded, will be provided. All Principal Investigator (PIs), site staff, and subjects will remain blinded throughout the study.

Sample Size Justification:

According to Corpechot 2018, the median percent change from baseline of ALP at Month 24 of BZF 400 mg [redacted]

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 International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the Sponsor's policies.

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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
ACR	albumin/creatinine ratio
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AFP	alpha-fetoprotein
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
[redacted]	
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAS	bile acid sequestrants
β-hCG	Beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
BZF	Bezafibrate
[redacted]	
C4	7α-hydroxy-4-cholesten-3-one
[redacted]	
CCDS	Core Company Data Sheet
CDCA	chenodeoxycholic acid
CI	confidence interval
C_{max}	peak (maximum) plasma concentration
CP	Child-Pugh
CK	creatine kinase
CRA	Clinical Research Associate
CRF	case report form
CRP	c-reactive protein
CS	clinically significant
DAP	data access plan
DB	double-blind

Abbreviation or Specialist Term	Explanation
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eAg-	hepatitis B e-antigen negative
eAg+	hepatitis B e-antigen positive
EASL	European Association for the Study of the Liver
EDC	electronic data capture
[redacted]	
EMA	European Medicines Agency
EODB	end of double-blind
EOS	end of study
[redacted]	
ET	early termination
FDA	US Food and Drug Administration
FDC	Fixed Dose Combination
FIS	fatigue impact scale
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
[redacted]	
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	healthcare provider
HCV	hepatitis C virus
HDLc	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity c-reactive protein
HSAC	Hepatic Safety Adjudication Committee
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

Abbreviation or Specialist Term	Explanation
IP	investigational product
IR	immediate release
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
IWRS	interactive web response system
LDLc	low-density lipoprotein cholesterol
LS	least squares
LTSE	long-term safety extension
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
mITT	modified Intent-to-Treat
[redacted]	
MRS	Mayo Risk Score
NASH	nonalcoholic steatohepatitis
[redacted]	
OCA	obeticholic acid
PBC	primary biliary cholangitis
[redacted]	
[redacted]	
PI	Principal Investigator
[redacted]	
PPAR	peroxisome proliferator-activated receptor
[redacted]	
PSC	primary sclerosing cholangitis
PT	prothrombin time
QD	once daily
SAE	serious adverse event
sAg-	hepatitis B surface antigen negative
sAg+	hepatitis B surface antigen positive
SAP	statistical analysis plan
SAR	suspected adverse reaction
SE	standard error
SmPC	Summary of Product Characteristics
SR	sustained release

Abbreviation or Specialist Term	Explanation
SSC	secondary sclerosing cholangitis
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T3	triiodothyronine
T4	thyroxine
TE	transient elastography
TEAE	treatment-emergent adverse event
TIPS	transjugular intrahepatic portosystemic shunts
T_{max}	time to C_{max}
TSH	thyroid-stimulating hormone
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

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) (Lu 2018); 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 (<0.6x ULN) are achieved (Murillo Perez 2020, Soret 2021). 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). 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 6α-ethyl derivative of the naturally occurring primary human bile acid CDCA, which is the endogenous ligand for FXR. FXR is a ligand-dependent transcription factor that is part of the nuclear receptor superfamily. FXR regulates a wide variety of target genes involved in the control of bile acid, lipid, and glucose homeostasis and in the regulation of immune responses.

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

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

The key mechanisms of action of OCA, including its choleretic, anti-inflammatory, and anti-fibrotic properties, underlie its hepatoprotective effects and result in attenuation of injury and improved liver function in a cholestatic liver disease such as PBC (Pellicciari 2005).

Fibrates exert potent anticholestatic effects through activation of PPARα 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 patients. In PBC, patients taking BZF showed a rapid and sustained decrease in ALP and a decrease in total bilirubin, and an increase in bilirubin levels in patients with cirrhotic liver disease was not observed (Corpechot 2018).

In a 2019 American Association for the Study of Liver Diseases (AASLD) conference, data on patients receiving BZF (400 mg) or placebo for a period of 21-days were presented. The primary endpoint was a 50% reduction of pruritus determined by VAS score. Seventy patients with a baseline VAS score of 5 out of 10 completed the trial (44 primary sclerosing cholangitis (PSC); 2 secondary sclerosing cholangitis (SSC); 24 PBC). BZF (n=37) led in 38% of the patients (38% in PSC, 36% in PBC) to ≥50% reduction of pruritus (VAS) whereas patients treated with placebo reached the primary endpoint in 12% (p=0.03). Patients 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% under BZF, but not under placebo (p=0.04) and correlated with reduction of the VAS pruritus score (p <0.001). Collectively, these data

demonstrate BZF is superior to placebo in improving pruritus in chronic cholestatic liver diseases such as PSC and PBC (de Vries et al, 2019).

5.3. Nonclinical Experience with Obeticholic Acid and Bezafibrate

5.3.1. Obeticholic Acid

Intercept Pharmaceuticals, Inc. (the Sponsor) has completed a standard battery of nonclinical safety pharmacology and toxicology studies for OCA. 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.

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

Refer to the latest version of the Fixed-Dose Combination (FDC) Investigator's Brochure for additional information regarding the nonclinical program for BZF.

5.4. Clinical Experience with Obeticholic Acid and Bezafibrate

The Sponsor has initiated a clinical development program to evaluate the safety and efficacy of BZF in combination with OCA in patients with PBC. The initial 3 studies include a Phase 1 study in healthy subjects (Study 747-123), a Phase 2 study (747-213) in subjects with PBC that is being conducted outside of the US, and a Phase 2 study conducted in the US, Canada, Turkey, Italy, and Argentina (Study 747-214) to evaluate the dose/exposure-response of the OCA+BZF combination and to provide further safety/tolerability information of the combination in the targeted population.

Study 747-123 is an ongoing, Phase 1, randomized, controlled study evaluating single-dose escalation of bezafibrate given alone, multiple-dose escalation of OCA and BZF given alone and in combination, and the relative bioavailability of OCA and BZF administered in a fixed dose combination tablet compared to each product administered separately in healthy subjects. This study has enrolled 132 healthy subjects, with planned completion by early 2024.

In addition to the Phase 2 Study 747-213 described herein, Study 747-214 is an ongoing, Phase 2a randomized, double-blind, active-control multicenter study, with an initial 3-month double-blind treatment period, followed by a Long-Term Safety Extension (LTSE) Period (up to 48 Weeks) being conducted in the US. The primary objective is to evaluate the efficacy, safety, and tolerability of OCA, administered alone or in combination with BZF, in subjects with PBC

who had an inadequate response or who are unable to tolerate UDCA. This study has been fully enrolled (31 subjects), with an LTSE currently ongoing.

Study 977-113 is a completed, Phase 1, open-label study of absorption, metabolism, and excretion of BZF in healthy male subjects. The study enrolled 8 healthy male subjects who received a single dose of 400 mg of [14C]-bezafibrate capsule(s) containing approximately 400 μCi, followed up by a 14-day inpatient evaluation period.

5.4.1. Obeticholic Acid

As of 26 May 2023, approximately 4616 subjects (3549 patients and 1067 healthy volunteers) have received OCA in clinical trials sponsored by Intercept (including ongoing Intercept sponsored clinical trials) and Sumitomo Dainippon Pharma Co., Ltd., (Intercept's former co-development partner in China, Korea, and Japan).

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.

OCA is also being evaluated in other indications, including biliary atresia.

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 patients 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 has a low volume of distribution, is extensively bound to serum albumin, and its erythrocyte uptake is minimal. Elimination is rapid. BZF is predominantly (about 50% of the dose) excreted in the urine as unchanged drug. Renal excretion is mostly by glomerular filtration (renal clearance is about 70 mL/min). In patients with impaired renal function, especially those patients in whom creatinine clearance (CLcr) is less than 60 mL/min, there is a marked increase in the systemic exposure of BZF. Systemic exposure increases further with decrease in renal function when CLcr is lower than 60 mL/min. When administered together with cholestyramine, the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values of BZF are reduced, indicating decreases in oral

absorption. This effect of cholestyramine can be minimized by waiting 2 hours after cholestyramine intake before administering 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 patients) that evaluated the efficacy and safety of BZF mono-therapy treatment in patients with PBC (Yin 2015) (Appendix B). In total, approximately 610 subjects with PBC have been treated with BZF (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 + UDCA), subjects treated with BZF + UDCA had a significantly higher rate of complete biochemical response (defined as normal levels of total bilirubin, alkaline phosphatase, aminotransferases, and albumin, and a normal prothrombin index) than subjects treated with placebo + UDCA (31% versus 0%) (Corpechot 2018).

Overall, 424 AEs were reported in 88 subjects (49% in the BZF group and 51% in the placebo group). A total of 39 serious adverse events (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. A total of 4 subjects (3 [6%] on BZF and 1 [2%] on placebo) had increases in aminotransferases that were more than 5x ULN and were significant enough to require treatment withdrawal. All AEs of elevated aminotransferases resolved within 3 months for the BZF subjects (spontaneously in 1 subject) or after administration of glucocorticoid (in 2 subjects with whom liver histologic features at baseline were suggestive of associated autoimmune hepatitis) (Corpechot 2018).

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

The absorption, metabolism, and excretion of BZF was evaluated in the Phase 1 Study 977-113 in healthy male subjects. The study enrolled 8 healthy male subjects who received a single dose of 400 mg of [14C]-bezafibrate capsule(s) containing approximately 400 µCi, followed up by a 14-day inpatient evaluation period. All subjects have completed the study and the final clinical study report is pending.

Refer to the latest version of the FDC Investigator's Brochure for additional information regarding the BZF clinical program.

5.5. Rationale for Study Design and Dose for Investigational Products

5.5.1. Rationale for Study Design

UDCA is widely accepted to be the first-line therapy for PBC. However, PBC may progress despite UDCA treatment, and UDCA is intolerable to a minority of patients. The 2017 EASL guidelines indicate that patients should continue to be evaluated for their risk of developing end-stage complications that may require treatments in addition to UDCA. For patients who respond to UDCA, an individualized approach is recommended, while the addition of second-line therapy is recommended for patients 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 patients with PBC who demonstrated no or partial response to UDCA. As such, OCA has been conditionally approved for patients with PBC in combination with UDCA for those with an inadequate response to UDCA or who are intolerant to UDCA.

A number of small studies and nonrandomized 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 patient 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 patients 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 patients on background UDCA therapy from the combination of BZF and OCA compared with OCA or BZF alone. In a recent 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 patients. 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).

A recent 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. The majority of subjects were women at least 50 years of age. The median ALP was 2.7x ULN. Pruritus occurred in 59% of subjects. Proven or predicted cirrhosis was 22%. The median duration of prior UDCA therapy was 4.1 years (range 1.0-24.8). The average UDCA dose was 15.4 (4.0) mg/kg/day (range 7.6-24.6) and 11 (19%) subjects had PBC-autoimmune hepatitis (AIH) overlap (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 triple therapies (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% to 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.

Bezafibrate therapy also has demonstrated benefit beyond improvements in liver function. In a recent AASLD Conference (2019), data on patients receiving BZF (400mg) or placebo for a period of 21-days was presented (de Vries et al, 2019). The primary endpoint was a 50% reduction of pruritus determined by VAS score. Seventy patients completed the trial (44 PSC, 2 SSC, 24 PBC). BZF (n=37) led in 38% of the patients (38% in PSC, 36% in PBC) to ≥50% reduction of pruritus (VAS) whereas patients treated with placebo reached the primary endpoint in 12% (p=0 03). Patients 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% under BZF but not under placebo (p=0.04) and correlated with reduction of the VAS pruritus score (p<0.001).

Taken together, these studies indicate triple therapy with fibrates, OCA, and UDCA improves biochemical liver tests and increases the rate of ALP normalization in patients with PBC and incomplete response to second-line therapy. The addition of BZF may improve the impact on pruritus.

EASL 2017 has recommended that UDCA, if tolerated, should be continued for life. Therefore, while the 747-213 study is designed to assess the combined effects of OCA and BZF, stable UDCA use will be allowed in this study for patients currently taking UDCA.

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 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 and 10 mg.

The double-blind (DB) Period of this study is being conducted for a minimum of 12 weeks (3 months). In the Phase 2 studies, the vast majority of the ALP and liver enzyme reductions were evident after 1 month of therapy. Accordingly, this study will evaluate the 10-mg OCA dose alone and in combination with BZF. To ensure that there is adequate exposure and time to produce a response at the OCA doses, all subjects will start with OCA 5 mg on Day 1 for 4 weeks; titration to OCA 10 mg is to occur at Week 4. The dose of 10 mg OCA once daily (QD) will continue through the end of the DB Period. Subjects who complete the DB Period will continue on DB assignment during the DB Follow-Up Period. Subjects will be held in the DB Follow-Up Period until the last subject enrolled completes Week 12 of the DB Period. At which point, all subjects will transition to the LTSE Period.

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 immediate release (IR) 200 mg tablet formulation administered up to 3 times daily (600 mg/day) or the sustained release (SR) 400 mg tablet formulation administered QD (400 mg/day).

SR 400 mg and IR 200 mg are the daily doses of marketed BZF being assessed in this study. The BZF dose-response data were obtained from patients with hyperlipidemia using triglycerides and/or cholesterol as response markers. The lowest available marketed BZF dosage is the 200-mg IR tablet, which has a relatively short 2.4-hour half-life. 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 dose of 200-mg/day BZF will be used as the low dose in this 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.

A significant effect of BZF in combination with UDCA on ALP was seen as early as 1 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 Period should be sufficient to see a significant change in ALP with the combination of OCA, BZF, and UDCA.

All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period.

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, 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 fixed-dose combination (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 2020, Soret 2019, and Smets 2021). Two recent studies have demonstrated that the combined use of OCA + BZF on background therapy with UDCA may have additive clinical benefit in patients with PBC compared with OCA or BZF alone (Smets 2020, Soret 2021).
3. Many PBC patients 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 patients has demonstrated normalization of biomarkers of liver function (ALP and bilirubin) (Smets 2019, Corpechot 2019).

A number of studies (approximately 610 subjects across more than 20 studies) have suggested that BZF as second-line therapy may reduce ALP levels in PBC patients who are non- or partial UDCA responders (Agrawal 2019) (Appendix B). 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 American Association for the Study of Liver Diseases (AASLD) guidance for the management of PBC states that fibrates can be considered as off-label alternatives for patients 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). Given evidence to support the notion that the mechanisms of action of OCA and BZF are complementary and suggest that OCA and BZF may have additive effects and thus potential benefit for PBC patients when used on background UDCA therapy (D'Amato 2020, Smets 2020, Soret 2019, Soret 2021).

Therefore, the Sponsor is conducting Study 747-213 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's 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 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.
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; IR = immediate release; SmPC = Summary of Product Characteristics; SR = sustained release.
Source: Bezalip Mono 400 mg SR Tablets, SmPC 2016

The overall safety profile of BZF is currently based on a combination of clinical study data and post-marketing experience in patients 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, bezafibrate 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% – 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.

BZF should not be dosed at the same time as cholestyramine in those patients whose medical conditions require it. When the combination of BZF SR 400 mg tablets with OCA are administered concurrently with resins, an interval of 4 hours should be maintained between the 2 drugs.

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

There is currently no safety information from controlled trials using BZF and OCA 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 bezafibrate and Ocaliva 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 patient population and indication for the treatment of severe hypertriglyceridaemia and mixed hyperlipidaemia. Decreased appetite and gastrointestinal disorders were the most common undesirable effects. Per the Summary of Product Characteristics, cholelithiasis is a labeled undesirable effect of BZF (very rare) (Bezalip Mono 2016, Bezalip Mono 2020, Bezafibrate Retard 2017, Bezafibrate 2016, Bezafibrate 2020) and has also been reported in OCA clinical studies at higher 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 patient with diffuse myalgias, muscle tenderness/weakness, or marked elevations in creatine phosphokinase levels, and dose adjustment may be needed in patients with impaired renal function. Patients 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 patients reporting these symptoms, and BZF therapy should be discontinued if markedly elevated CK levels (≥5x ULN with symptoms of rhabdomyolysis) occur or myopathy is diagnosed (Table 5). 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.

Despite these rare and known effects, 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

To assess the effects of the combination of OCA and BZF in comparison to BZF alone in subjects with PBC on the following:

- Biochemical disease markers, including ALP, GGT, ALT, AST, total and conjugated bilirubin, and a lipid panel
- Biomarkers of bile acid synthesis and homeostasis, including 7α-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

This Phase 2, proof-of-concept, randomized, double-blind, parallel-group study will evaluate the efficacy, safety, and tolerability of OCA (5 mg and 10 mg) administered in combination with 2 different BZF doses (200 mg and 400 mg) or BZF alone (at two doses, 200 mg and 400 mg) in up to 72 subjects with PBC over at least 12 weeks.

Protocol Version 2 and 3 Overview of Differences: Protocol Version 2 had a 3-arm design (Group 1, OCA 5 mg to 10 mg; Group 2, OCA 5 mg to 10 mg + BZF 200 mg IR; Group 3, OCA 5 mg to 10 mg + BZF 400 mg SR), whereas Protocol Version 3 onwards has a 4-arm design: Group 1 (Treatment A: BZF 200 mg IR); Group 2 (Treatment B: BZF 400 mg SR); Group 3 (Treatment C: OCA 5 mg to 10 mg + BZF 200 mg IR); and Group 4 (Treatment D: OCA 5 mg to 10 mg + BZF 400 mg SR). Subjects enrolled under Protocol Version 2 will remain on the initial study arm/treatment regimen (one of 3 treatment arms) throughout the DB, DB Follow-Up, and LTSE periods while completing the visits and assessments described under the current protocol approved at the site. Upon completion of Visit 10 of the DB Follow-up period, subjects enrolled under Protocol Version 2 will transition to the LTSE period.

Screening Period (2 weeks and up to 8 weeks): Subjects will be screened for a period of 2 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 Treatment Period (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 200 mg IR once daily [QD]), Treatment B (BZF 400 mg SR tablet QD), Treatment C (OCA 5 mg→10 mg QD + BZF 200 mg IR QD), or Treatment D (OCA 5 mg→10 mg QD + BZF 400 mg SR QD).

Subjects who are randomized to combination groups will receive OCA 5 mg QD from Day 1 to the day before the Week 4 Visit, followed by OCA 10 mg QD from the Week 4 Visit through the end of the study. To preserve the study blind, appearance-matched placebo tablets for OCA and/or BZF will be administered to subjects in each treatment group from Day 1 to Week 12 as shown in the study design diagrams for the DB and LTSE periods. Subjects will be instructed to begin dosing on Day 1 and to take investigational product at approximately the same time each day (morning dosing for the entire 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 the study. At study visits, all doses of investigational product will be administered at the clinic. Subjects are instructed to take investigational product with a meal onsite after all procedures have been completed or may take at home if dizziness is a concern, following a fast of at least 8 hours before dosing. A low-fat meal or meal replacement drink will be given with investigational product administration at visits with serial PK collections (see Section 14.1).

Subjects will be maintained on the DB dose and will transition to DB Follow-Up Period on the same dose. All subjects will be held in the DB Follow-Up Period until the last subject completes Week 12 of the DB period.

Randomization will be stratified by:

- Total bilirubin level (≤0.7x or >0.7x ULN but <2x ULN)

- ALP ≥1.5x ULN but ≤1.67x ULN (not more than 25% of subjects enrolled)
- ALP >1.67x ULN (remaining subjects enrolled)

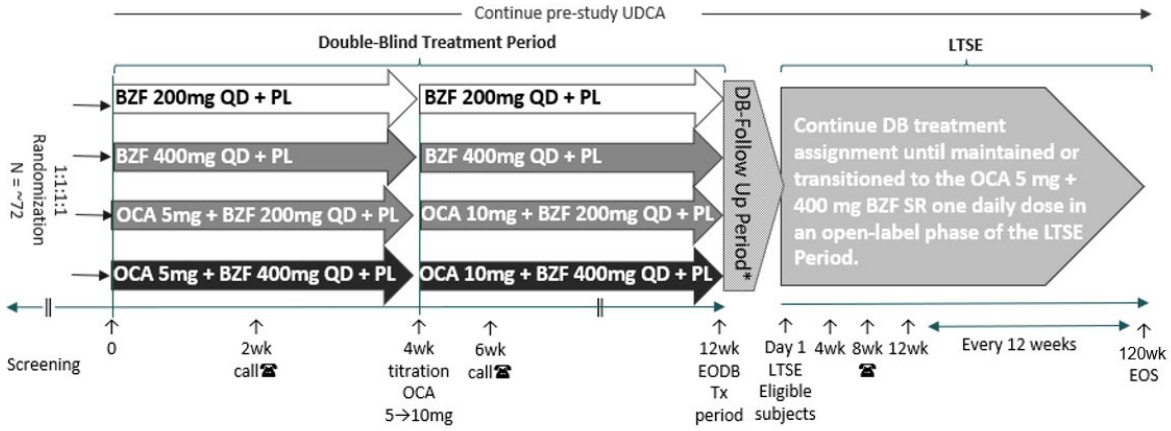
Note: The total subject population will also include up to 10% of subjects with ALP >5x ULN.

After the Day 1 Visit, subsequent clinic visits during the DB Period will occur at approximately Weeks 4, 8, and 12 (efficacy, safety, tolerability, and PK will be assessed) and then every 12 weeks for the assessment of efficacy, safety, and tolerability. PK will not be assessed after Week 12. Subjects will also be contacted by telephone at Weeks 2 and 6 (± 5 days) to assess for occurrence of any adverse events (AEs), changes to concomitant medications and/or new medications that have been initiated, and medical/surgical procedures, and to verify that the subject is dosing as directed. During the DB Period, an interim analysis will be performed when at least 40 subjects have completed the Week 12 visit.

LTSE Period (up to 120 weeks): All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period.

All site staff will maintain study blind until the study is moved to an open-label phase of the LTSE Period. Safety and laboratory assessments will be evaluated at clinic visits once every 12 weeks and up to Week 120.

Figure 1: Study Design for the Double-Blind, DB Follow-Up and LTSE Periods (Study 747-213)



BZF = bezafibrate; DB = double-blind; EODB = end of DB; EOS = end of study/end of LTSE Period; FDC = fixed dose combination; LTSE = long-term safety extension; OCA = obeticholic acid; QD = once daily; SR=sustained release; UDCA = ursodeoxycholic acid. PL = Placebo = either OCA or BZF tablets.

Note: *DB Follow-Up Period: Subjects will move into the DB Follow-Up Period and remain in this period until the last subject finishes the DB Period.

Note: The Screening Period is 2 weeks to a maximum of 8 weeks.

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

Note: All patients will transition to LTSE Day 1 at the same time from either the DB Period (Week 12; last subject completing the DB period) or the DB Follow-Up Period (remainder of all subjects).

Please refer to Appendix A for a description of treatment arms and study design for subjects who were randomized under Protocol Version 2.

7.1.2. Schedule of Study Procedures

Table 3: Schedule of Study Procedures During the Double-Blind and DB Follow-Up Periods

	Screening Period [a]		Double-Blind Period						DB Follow-Up Period, Every 12 weeks	EODB Treatment/ ET[b]
	Screening Visit 1	Screening Visit 2	Day 1	Week 2 Phone Call	Week 4	Week 6 Phone Call	Week 8	Week 12		
Visit Window (Relative to Visit Day)	2 weeks to maximum of 8 weeks			±5 days	±5 days	±5 days	±5 days	±2 weeks	±2 weeks	
STUDY PROCEDURES										
Fast ≥8 Hours Prior to Visit[c]		X	X		X		X	X	X	
Informed Consent Form	X									
Medical/Surgical History and PBC History/Demographics	X	X	X[d]							
Myopathy Evaluation and Monitoring[q]	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications[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									
Weight (including BMI and waist-hip ratio)[q]	X		X		X		X	X	X	X
Vital Signs[f]	X		X		X		X	X	X	X
12-Lead Electrocardiogram	X							X	X	X
AEs[g]	X	X	X	X	X	X	X	X	X	X
CP Assessment[h]	X	X	X		X		X	X	X	X
[redacted]										
Randomization/Treatment Assigned			X							
[redacted]										
Dispense/Administer Investigational Products			X		X		X	X	X	
Assess Investigational				X	X	X	X	X	X	X

	Screening Period [a]		Double-Blind Period						DB Follow-Up Period, Every 12 weeks	EODB Treatment/ ET[b]
	Screening Visit 1	Screening Visit 2	Day 1	Week 2 Phone Call	Week 4	Week 6 Phone Call	Week 8	Week 12		
Visit Window (Relative to Visit Day)	**2 weeks to maximum of 8 weeks**			**±5 days**	**±5 days**	**±5 days**	**±5 days**	**±2 weeks**	**±2 weeks**	
Products Accountability & Compliance										
CLINICAL AND LABORATORY EVALUATIONS										
Serum Chemistry, Hematology, Coagulation[j,p]	X	X	X		X		X	X	X	X
Thyroid Hormones (Free T3, free T4, and TSH)	X							X	X	X
Virology (HCV/HBsAg)	X									
Urinalysis	X				X			X	X	X
Urine-Based β-hCG Pregnancy Test[k]	X	X	X		X		X	X	X	X
[redacted]										
C4 and bile acids			X		X		X	X	X	X
[redacted]										
[redacted]										
[redacted]										

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted]; AST = aspartate aminotransferase; AUC = area under the concentration-time curve; β-hCG = beta-human chorionic gonadotropin; BZF = bezafibrate; C4 = 7α-hydroxy-4-cholesten-3-one; C_{max} = peak (maximum) plasma concentration; CP = Child-Pugh; CK=creatine kinase; DB = double-blind; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; [redacted]; EODB = end of DB; [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; [redacted]; OCA = obeticholic acid; [redacted]; PI=Principal Investigator; [redacted]; $t_{½}$ = half-life ; T3 = triiodothyronine; T4 = thyroxine; TE = transient elastography; TSH = thyroid-stimulating hormone; [redacted]; WHR=Waist to hip ratio.

Note: Unscheduled visits should occur as needed in the event of signs or symptoms of potential hepatic injury or hepatic decompensation or if laboratory alerts have been triggered.

[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] EODB Treatment Visit occurs when a subject reaches the final visit in the DB Treatment Period and is not going into the LTSE period. If a subject is continuing into the LTSE period then the EODB Treatment visit is not done and the subject will complete the LTSE Day 1 visit instead of the EODB Treatment visit. If a subject discontinues treatment during the DB period then they should complete the ET Visit as near as possible to last dose taken. Subjects who discontinue treatment should then continue coming in for their scheduled visits until the end of the DB Treatment Period where they would complete the EODB Treatment visit and finish the study.

[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 within 8 hours, 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. Subjects are instructed to take IP with a meal at site after all procedures (including PK days) have been completed or may take at home if dizziness is a concern.

[d] Assessment of baseline pruritus only.

[e] 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.

[f] Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting for 3 minutes.

[g] 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.

[h] CP Score will be calculated based on central laboratory evaluations and a targeted assessment of ascites and hepatic encephalopathy. Scores will be calculated and recorded on the eCRF (see Section 7.4.4)

[i] [redacted] will be calculated from serum chemistry and other parameters collected at the same visit with scores recorded on the eCRF.

[j] To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, and total and conjugated bilirubin.

[k] 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 test (serum quantitative β-hCG) must be performed at the central laboratory. If the confirmatory blood test is also positive, the subject may not continue in the study. (Additional testing may be conducted where required, regionally).

[l] To be performed only if test is available at qualified sites.

[redacted]

[n] [redacted] and will be calculated by the Sponsor.

[o] [redacted] will be calculated from serum chemistry and other parameters (scores to be calculated by the Sponsor).

[p] At Screening, check baseline CK: If ≥5x 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 symptoms of myopathy at any point during the study, CK values must be checked. A CK ≥5x ULN or ≥3x ULN with symptoms consistent with rhabdomyolysis will require IP interruption. Laboratory values including CK and creatinine will be closely monitored every 2 weeks until values return to baseline levels (see Table 5).

[q] Waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurement.

[r] [redacted]

[s] [redacted] are only to be completed for subjects enrolling on or after protocol Version 4.

Table 4: Schedule of Study Procedures During the Long-Term Safety Extension Period

	Long-Term Safety Extension Period												
	LTSE Day 1[a]	**LTSE Week 4**	**LTSE Week 8 Phone Call**	**LTSE Week 12**	**LTSE Week 24**	**LTSE Week 36**	**LTSE Week 48**	**LTSE Week 60**	**LTSE Week 72**	**LTSE Week 84**	**LTSE Week 96**	**LTSE Week 108**	**LTSE Week 120/ EOS[o]**
Visit Window		**±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[b]	X	X		X	X	X	X	X	X	X	X	X	X
Medical/Surgical History and Eligibility	X												
Myopathy Evaluation and Monitoring[j]	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
Physical Examination	X			X	X	X	X	X	X	X	X	X	X
Weight (including BMI and WHR)[k]	X	X		X	X	X	X	X	X	X	X	X	X
Vital Signs[c]	X	X		X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X												X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
CP Assessment[d]	X	X		X	X	X	X	X	X	X	X	X	X
[redacted]													
Dispense/Administer Investigational Products	X	X		X	X	X	X	X	X	X	X	X	

	Long-Term Safety Extension Period												
	LTSE Day 1[a]	**LTSE Week 4**	**LTSE Week 8 Phone Call**	**LTSE Week 12**	**LTSE Week 24**	**LTSE Week 36**	**LTSE Week 48**	**LTSE Week 60**	**LTSE Week 72**	**LTSE Week 84**	**LTSE Week 96**	**LTSE Week 108**	**LTSE Week 120/ EOS[o]**
Visit Window		**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±2 weeks**
Assess Investigational Product Accountability & Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X
CLINICAL AND LABORATORY EVALUATIONS													
Serum Chemistry, Hematology, Coagulation[h]	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		
Urinalysis	X	X		X	X		X		X		X		X
Urine-Based β-hCG Pregnancy Test[i]	X	X		X	X	X	X	X	X	X	X	X	X
[redacted]													
C4 and bile acids	X	X			X		X		X		X		
[redacted]													

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CP = Child-Pugh; DB = double-blind; eCRF = electronic case report form; EOS = end of study; [redacted]; IP = investigational product; LTSE = long-term safety extension; [redacted]; WHR = waist to hip ratio

Note: Week 120 is the last visit in the LTSE Period. Week 120 is the EOS. If a subject discontinues treatment or discontinues the study before Week 120, they should come in for the EOS Visit which will be their final visit. Week 120 and EOS have the same assessments required.

Note: Unscheduled visits should occur as needed in the event of signs or symptoms of potential hepatic injury or hepatic decompensation or if laboratory alerts have been triggered.

[a] Subjects will be held in the DB Follow-Up Period until the last subject finishes the DB Period. At that point, all subjects will transition to the LTSE Period. LTSE Day 1 will be the last visit in the DB Period (Week 12) or the DB Follow-Up Period.

[b] The subject should be instructed to fast overnight (at least 8 hours) prior to each visit, but water is permitted. Subjects are instructed to take IP with a meal at site after all procedures have been completed or may take at home if dizziness is a concern.

[c] Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting for 3 minutes.

[d] CP Score will be calculated based on central laboratory evaluations and a targeted assessment of ascites and hepatic encephalopathy. Scores will be calculated and recorded on the eCRF (see Section 7.4.4)
[e] [redacted] will be calculated based on serum chemistry and other parameters collected at the same visit with scores recorded on the eCRF.
[f] [redacted] and will be calculated by the Sponsor.
[g] [redacted] will be calculated from serum chemistry and other parameters (scores to be calculated by the Sponsor).
[h] To include ALP, CK, creatinine (including eGFR), GGT, ALT, AST, and total and conjugated bilirubin, [redacted]
[i] 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 test (serum quantitative β-hCG) must be performed at the central laboratory. If the confirmatory blood test is also positive, the subject may not continue in the study. Additional testing may be conducted where required, regionally.
[j] Refer to Section 7.4.4.3 for instructions.
[k] Waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurement.
[n] To be performed only if test is available at qualified sites.
[o] If a subject discontinues treatment, they should complete the EOS visit as near as possible to last dose taken.
[p] [redacted] are only to be completed for subjects enrolling on or after protocol Version 4.

7.1.3. Study Duration

The duration of treatment per subject will be a minimum of approximately 108 weeks, which includes a 12-week DB Period, followed by 120 weeks of treatment during the LTSE Period. Subjects will remain in the DB Follow-Up Period until the last subject enrolled reaches Week 12 at which point all subjects will transition to the LTSE Period. The maximum length of time that a subject will be in the study will depend on the length of the enrolment period.

7.2. Number of Subjects

Up to 72 subjects (18 per group) will be enrolled and randomized in a 1:1:1:1 ratio to 1 of 4 treatment arms (Treatments A:B:C:D).

7.3. Planned Dosing Regimen

Treatment assignment**s** for protocol Version 2 are listed in Appendix A.

Subjects will be randomly assigned in a 1:1:1:1 ratio to receive one of the following treatments during the DB Period:

Treatment Arm	DB Treatment Morning Dose Regimen
Treatment A: BZF 200 mg IR tablet QD	OCA 5 mg placebo tablet (Weeks 0 to 4) OCA 10 mg placebo tablet (Week 4 to end of DB treatment) **BZF 200 mg IR tablet** BZF 400 mg SR placebo tablet
Treatment B: BZF 400 mg SR tablet QD	OCA 5 mg placebo tablet (Weeks 0 to 4) OCA 10 mg placebo tablet (Week 4 to end of DB treatment) **BZF 400 mg SR tablet** BZF 200 mg IR placebo tablet
Treatment C: OCA 5 mg→10 mg QD + BZF 200 mg IR QD	**OCA 5 mg tablet (Weeks 0 to 4)** **OCA 10 mg tablet (Week 4 to end of DB treatment)** **BZF 200 mg IR tablet** BZF 400 mg SR placebo tablet
Treatment D: OCA 5 mg→10 mg QD + BZF 400 mg SR QD	**OCA 5 mg tablet (Weeks 0 to 4)** **OCA 10 mg tablet (Week 4 to end of DB treatment)** BZF 200 mg IR placebo tablet **BZF 400 mg SR tablet**

BZF = bezafibrate; DB = double-blind; IR = immediate release; OCA = obeticholic acid; QD = once daily; SR = sustained release
Active treatments are in bold text.

All randomized subjects will enter the 12-week DB Period and upon completion, will be held in the DB Follow-Up Period until all subjects complete the DB Period.

Subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period

until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period.

7.4. Monitoring and Management of Potential 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 and [redacted] will be reviewed at each visit where labs are drawn (Section 7.4.4 and Section 15.2.1). 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/or muscular 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 electronic case report form (eCRF) or the SAE eCRFs (Section 15.1.4.1 and Section 15.1.4.2), and (5) contact with the Medical Monitor (Section 15.1.5).

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

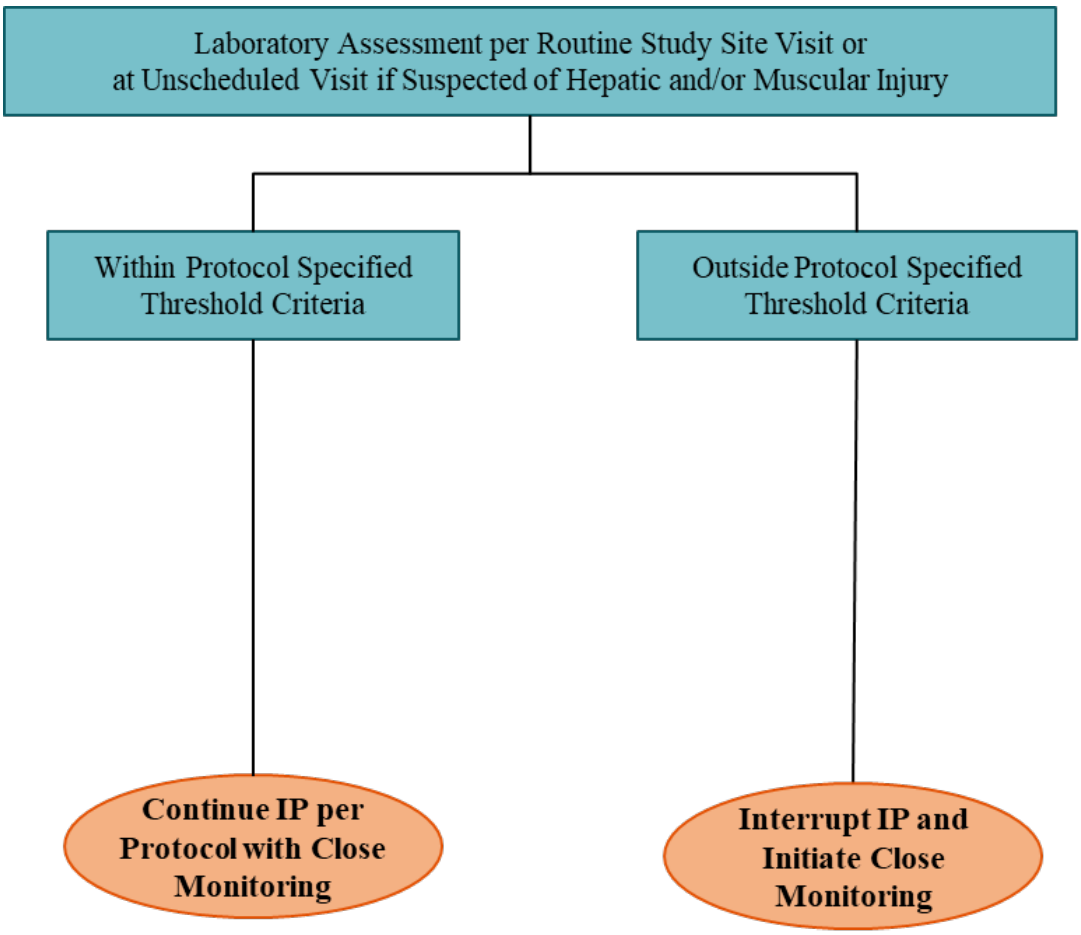
Liver biochemistry and serum CK will be assessed to evaluate for potential hepatic and/or muscular injury or hepatic decompensation. These assessments will be performed at:

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

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

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger investigational product interruption are summarized in Table 5.

Figure 2: Management Algorithm for Potential Hepatic and/or Muscular Injury



ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = gamma glutamyl transferase; INR = international normalized ratio; IP = Investigational Product; [redacted].
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 (Table 5).

Table 5: Laboratory Criteria for Monitoring of Potential Hepatic and Muscular Injury for 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)	Yes
ALT or AST Normal	ALT or AST ≥3x ULN and TB ≥2x BL	Yes or No
	ALT or AST ≥3x ULN and INR >1.5	Yes or No
	ALT or AST ≥5x ULN and Any TB	Yes or No
ALT or AST Elevated	ALT or AST ≥2x BL and TB ≥2x BL	Yes or No
	ALT or AST ≥2x BL and INR >1.5	Yes or No
	ALT or AST ≥3x BL (or ≥300 U/L, whichever occurs first) and Any TB	Yes or No
TB ≤ULN	TB ≥2x BL and >ULN	Yes or No
TB >ULN	TB ≥1.5x BL or ≥3.0 mg/dL, whichever occurs first	Yes or No
ALP ≤ULN	ALP ≥2x BL and >ULN	Yes or No
ALP >ULN	ALP ≥2x BL or ≥1000 U/L, whichever occurs first	Yes or No
CK	≥5x ULN or ≥3x ULN with symptoms of rhabdomyolysis[d,e]	N/A

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; CK = creatine kinase; DILI = drug-induced liver injury; GGT = gamma glutamyl transferase; INR = international normalized ratio; IP = investigational product; N/A = not applicable; 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 severe fatigue or significant worsening of baseline fatigue; new onset severe pruritus or significant worsening on baseline pruritus; nausea, vomiting, right upper quadrant 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 or sore muscles; dark urine; fever; tachycardia; nausea and vomiting; confusion; dehydration; or abdominal pain.

[e] If IP interrupted due to CK trigger, closely monitor CK and creatinine/renal function in addition to liver biochemistries with close monitoring as above; same criteria apply to considering re-initiation of IP. CK levels should be assessed in patients reporting symptoms of rhabdomyolysis, and BZF therapy should be discontinued if markedly elevated CK levels (≥5x ULN) occur or myopathy is diagnosed.

It should be noted that it is difficult to recognize every potential 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 Period, monitoring will occur on a bi-monthly basis from Day 1. Subjects who experience a decompensation event during the DB Period will not be eligible to enroll in the LTSE.

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

- Evidence of portal hypertension, defined as platelet count <150,000/µL
- 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 µmol/L])
  - [redacted]
  - 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. The Investigator should ensure all lab data is entered into the eCRF. 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		None	Mild	Moderate-Severe
Hepatic encephalopathy[a]		No	Grade 1 or 2	Grade 3 or 4

CP = Child-Pugh; 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 or asymptomatic esophageal varices)
  - Ascites
  - Radiological evidence of cirrhosis (e.g., nodular liver or enlargement of portal vein and splenomegaly)
- Combined low platelet count (<150,000/µL) 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 by the Sponsor 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 ≥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 ≥5x ULN or ≥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.

Additionally, investigational product should also be discontinued in the following instances:

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

7.6. Dosage Adjustment Criteria

7.6.1. Double-Blind and Double-Blind Follow-Up Periods

With an exception of the planned dose of 5 mg OCA from Week 1 through Week 4 in the combination treatment groups, dosages for OCA 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 15.1.3.1.

In the event of tolerability issues such as pruritus or myalgia, the dosing of all investigational product 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 DB Period should come in for an ET Visit as close as possible to the last dose taken. Once the ET visit has been completed the subject should continue coming in for their original scheduled visits until the end of the DB Period where they would complete the EODB Treatment 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 Period

All eligible, randomized subjects will enter the 12-week DB Period and will be held in the DB Follow-Up Period until the last subject completes the DB Period. All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period. Details of the move to the open-label phase of the LTSE Period will be provided in the Statistical Analysis Plan (SAP).

Dose frequency may be modified for the management of pruritus or other safety findings as described in Section 15.1.3.1. 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 period should come in 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 should continue this as a concomitant medication for the entirety of the LTSE Period 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 55 to 85 global study sites with experience in treating patients with PBC. Prospective subjects will be identified primarily from the hospital and/or physician's database of patients with PBC or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international PBC patient societies, forums, or networks.

8.1.1. Subject Inclusion Criteria

1. A definite or probable diagnosis of PBC (consistent with the EASL and the AASLD guidelines [Lindor 2009, 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 (≤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 ≥1.5x ULN but ≤1.67x ULN (will not exceed 25% of subjects enrolled in the study)
    - ALP >1.67x ULN (including up to 10% of subjects with ALP >5x ULN)

- Total bilirubin >ULN but <2x 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. Highly effective methods of contraception are as follows:
    - Intrauterine device
        - intrauterine device (IUD)
        - intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomy (partner)
    - Combined (estrogen and progestogen containing) hormonal contraception (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 if in line with the preferred and usual lifestyle of the subject, 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 Period.
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 deoxyribonucleic acid (DNA) negative) may be included in this study after consultation with the Medical Monitor.
  - Subjects should be excluded if positive HBV DNA or HCV ribonucleic acid (RNA)
- Primary sclerosing cholangitis
- Alcoholic liver disease
- Definite autoimmune liver disease or PBC-AIH overlap
- NASH
- Gilbert's Syndrome
- 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 or asymptomatic esophageal varices)
     - Ascites/hepatic hydrothorax
     - Spontaneous bacterial peritonitis
     - Hepatic encephalopathy
     - Jaundice (with total bilirubin >3 mg/dL [>51.3 μmol/L])
   - Biochemical evidence of hepatic impairment, hepatic decompensation, or injury including at least one of the following:
     - Total bilirubin >3 mg/dL (>51.3 μmol/L)
     - INR >1.7
     - Albumin <3.5 g/dL
     - MELD >12

  - ALT >5x ULN
- Known or suspected HCC
- Prior trans-jugular intrahepatic portosystemic or peritoneovenous shunt procedure
- Hepatorenal syndrome (Type I or Type II) or serum creatinine >1.5 mg/dL (135 µmol/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 remove (e.g., via ERCP) and cholecystectomy
    - Any size symptomatic gallbladder polyp
    - Gallbladder polyp >5 mm
7. History of acute or current pancreatitis
8. History of drug-induced myopathy
9. Chronic Kidney Disease (serum creatinine >1.5 mg/dL [>135 µmol/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 or >470 milliseconds for females
13. Severe pruritus, as defined in Table 12, 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. If female, known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating

16. 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
17. 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 or lipid-lowering agents, budesonide and other systemic corticosteroids, monoamine oxidase inhibitors (MAOIs), and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, and nitrofurantoin)
18. 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
19. Participation in a study of another investigational medicine or device within 30 days before Screening
20. Treatment with commercially available OCA or other FXR agonists, or participation in a previous study involving OCA within 3 months before Screening
21. Unable to tolerate BZF, other fibrates, known photoallergic or phototoxic reactions to BZF or other fibrates, treatment with commercially available fibrates, or participation in a previous study involving fibrates or PPAR-agonists within 3 months before Screening
22. 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).
23. 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
24. Blood or plasma donation within 30 days before Day 1
25. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain
26. A CK value at Screening ≥5x ULN or any abnormal laboratory value that is considered CS in the opinion of the Investigator and Sponsor (at either Screening visit)
27. 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 (including total cholesterol above >10 mmol/l)

8.2. Subject Withdrawal Criteria

Subjects who discontinue from investigational product are expected to continue in the study during the DB Period (and DB Follow-Up Period) 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 and DB Follow-Up Periods, refer to Section 9.7.7.

Subjects who are discontinued from investigational product during the LTSE Period 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 ≥Grade 3 in severity using criteria outlined in Section 15.1.3 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 Period or DB Follow-Up Period; the subject should not be allowed to enter the LTSE Period.

8.2.1.2. Pregnancy

If a female subject becomes pregnant, she must discontinue treatment with investigational product immediately but should continue with the study visit schedule. 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 Period or DB Follow-Up Period; however, subjects are free to discontinue at any time. Subjects who discontinue investigational product before completing the DB Period or DB Follow-Up Period are encouraged to also continue to follow the regular visit schedule through to EODB Treatment/ET. EODB treatment/ET procedures should only be conducted if the subject withdraws consent during the DB Period or DB Follow-Up Period or discontinues treatment (see Section 9.7.7).

Subjects who discontinue investigational product during the LTSE Period will need to come in for the 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 patient 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 return to the clinic for a study visit, and the Investigator ceases to have contact with the subject, he or she will be withdrawn from the study. 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 return for 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 and DB Follow-Up Periods: If a subject is withdrawn from the study early (regardless of the cause), all of the EODB Treatment/ET treatment evaluations are to be performed at the time of withdrawal, to the extent possible.

LTSE Period: 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.

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:

- Placebo OCA 5 mg and 10 mg tablets
- OCA 5 mg and 10 mg tablets
- BZF 200 mg IR tablet and 400 mg SR tablet
- Placebo BZF 200 mg IR tablet and 400 mg SR 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 (morning dosing with breakfast is preferred to align with all study visits) (including UDCA). 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.

At each study visit where the daily dose of investigational product is administered at the site, all assessments must be completed before administration of investigational product, except for the serial PK samples. Subjects are instructed to take investigational product with a meal onsite after all procedures have been completed or may take at home if dizziness is a concern. A low-fat meal or meal replacement drink will be given with investigational product administration at visits with serial PK collections during the DB Period (see Section 14.1).

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. Note that on days when blood is drawn for PK samples, concomitant medications should be taken after the final PK sample is taken (i.e., 6 hours post dosing).

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 coumarin-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

Subjects taking BAS (including cholestyramine and its derivatives, colestipol, colesevelam, or other BAS) or aluminum hydroxide- or smectite-containing antacids should refrain from using these drugs for the management of pruritus during the trial. The use of BAS may alter the interpretation of the effects of BZF on pruritus. If taking a bile acid binding resin, take OCA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

9.2.6. Estrogens

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

9.2.7. Drug-Drug Interaction

<u>OCA</u>

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 exposure of sensitive CYP2C9 probe, warfarin, exposure, or elicit pharmacokinetic drug-drug interaction, slight decreases in International Normalized Ratio were observed suggesting a potential to alter 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 definitely determined that the prothrombin level has been 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. Patients 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 patients 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 Investigators 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 patients receiving immuno-suppressant therapy and concomitant BZF. Renal function should be closely monitored in these patients and in the event of relevant significant changes in laboratory parameters, BZF should be discontinued.

Insulin and sulphonylurea: serious hypoglycaemia may result in the combinatory use of BZF and hypoglycaemic agents.

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

Resins: When BZF is used concurrently with cholestyramine or any other resin, an interval of at least 2 hours should be maintained between the 2 drugs, 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 patients 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 patients 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 return them to the Investigator at the indicated visits in Table 3. 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, randomized manner. Enrolled subjects will be randomized in a 1:1:1:1 ratio to one of the following treatment groups:

Treatment A: BZF 200 mg IR tablet QD	OCA 5 mg placebo tablet (Weeks 0 to 4) OCA 10 mg placebo tablet (Week 4 to end of DB treatment) BZF 200 mg IR tablet BZF 400 mg SR placebo tablet
Treatment B: BZF 400 mg SR tablet QD	OCA 5 mg placebo tablet (Weeks 0 to 4) OCA 10 mg placebo tablet (Week 4 to end of DB treatment) BZF 400 mg SR tablet BZF 200 mg IR placebo tablet
Treatment C: OCA 5 mg→10 mg QD + BZF 200 mg IR QD	OCA 5 mg tablet (Weeks 0 to 4) OCA 10 mg tablet (Week 4 to end of DB treatment) BZF 200 mg IR tablet BZF 400 mg SR placebo tablet
Treatment D: OCA 5 mg→10 mg QD + BZF 400 mg SR QD	OCA 5 mg tablet (Weeks 0 to 4) OCA 10 mg tablet (Week 4 to end of DB treatment) BZF 200 mg IR placebo tablet BZF 400 mg SR tablet

BZF = bezafibrate; DB = double-blind; IR = immediate release; OCA = obeticholic acid; QD = once daily; SR = sustained release.

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 by:

- Total bilirubin level (≤0.7x or >0.7x ULN but <2x ULN)
- ALP ≥1.5x ULN but ≤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 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 patient 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., bottle numbers and/or kit number allocated) while maintaining the study blind.

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

9.4.2. Blinding

The Sponsor will use data output from interim analyses from the DB Period for purposes of regulatory interactions and subsequent Phase 3 trial design planning. The interim analysis will be conducted by a Sponsor sub-team that will not be part of the study level activities. The Data Analysis Plan (DAP) will specify the make-up of the Sponsor sub-team and the appropriate data fire-walls to ensure data-integrity. The SAP will specify the methods for the interim analyses (see Section 16.7).

Additional Rolling Interim Analysis

The Sponsor will have the option to perform an additional unblinded rolling analysis of efficacy, PK, and safety data throughout the DB Period. Details of the unblinding and DAP, including Sponsor staff that will be unblinded, will be provided.

9.4.3. Emergency Unblinding Procedures

Treatment assignments for individual subjects will be made available to the Investigator and the Medical Monitor for medical emergency use only through the IWRS system. When possible, the Medical Monitor should be consulted in the event that 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 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 except serial PK 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 for the DB Period and in Table 4 for the LTSE Period. 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 her/his future medical treatment will not be compromised by participation in the study and that he or she can withdraw from the study at any time. The 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 ICFs 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 physical examination
- Measure height and record weight and 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted] (to be calculated by the Sponsor)
- [redacted]
- 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 (laboratory values may be repeated within 8 weeks). The most recent laboratory value should be used to confirm Screening requirements.
  - Virology: HCV/HBsAg
  - 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. 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.

- 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:

- 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
- Record concomitant medications
- Verify inclusion and exclusion criteria for eligibility
- Calculations will be performed by the Sponsor or designee for the following:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted] (to be calculated by the Sponsor)
- 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
- Perform a urine-based beta human chorionic gonadotropin (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 1 Procedures (Randomization)

All Day 1 procedures should be performed prior to dosing (the maximum time from Screening Visit 1 to Day 1 should be 8 weeks). Subjects are instructed to be fasted at least for 8 hours before dosing.

Day 1 Visit procedures for all subjects are as follows:

- 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 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 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted]
  - [redacted] (to be calculated by the Sponsor)
- [redacted]
- Access to IWRS for subject randomization/treatment assignment
- [redacted] only applicable for subjects enrolling on or after protocol Version 4
- Dispense/administer investigational products (during clinic visit)
- 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.
  - [redacted]
  - [redacted]
  - C4 and bile acids
  - [redacted]
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- Remind subject to fast for at least 8 hours prior to next dosing visit

9.7.4. Week 2 and Week 6 (Telephone Visits)

Week 2 and Week 6 visits will be conducted by telephone call. Subjects will be contacted for the following:

- Assess investigational product accountability and compliance
- Record concomitant medications
- Assess AEs
- Monitor for potential myopathy

9.7.5. Week 4, Week 8, and Week 12

The following procedures will be performed at Week 4, Week 8, and Week 12:

- 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 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 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted]
  - [redacted] (to be calculated by the Sponsor)
- [redacted] (at qualifying sites only)
- [redacted]
- Perform standard 12-lead ECG (Week 12 only)
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)

- Assess investigational products accountability and compliance
- Dispense/administer investigational products
- 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
  - Thyroid hormones: free T3, free T4, and TSH (Week 12 only)
  - [redacted]
  - [redacted]
  - C4 and bile acids
- Urinalysis (Week 4 and Week 12 only)
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- Subjects need to be in fasting condition for at least 8 hours prior to collection of PK samples. Obtain serial (Weeks 4 and 8) or trough (predose; Week 12) PK samples (see Table 9 for the PK windows and Section 14.1 for the timing of PK blood samples). A meal replacement drink or low-fat meal will be provided with investigational product administration (Weeks 4 and 8) and after the 4-hour PK sample is collected (Weeks 4 and 8).

9.7.6. Double-Blind Follow-Up Period Follow-up Visits (Every 12 Weeks)

The following procedures will be performed at each follow-up visit (every 12 weeks):

- 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 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
- Physical examination
- Record weight and BMI and WHR
- 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:

  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by Sponsor)
  - [redacted]
  - [redacted] (to be calculated by Sponsor)
- [redacted]
- [redacted]
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)
- Assess product accountability/compliance
- Dispense/administer investigational products
- 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
  - Thyroid hormones: free T3, free T4, and TSH
  - [redacted]
  - [redacted]
  - C4 and bile acids
- Urinalysis
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- Remind subject to fast at least 8 hours prior to next dosing visit.

9.7.7. End of Double-Blind Treatment/Early Termination Procedures for Subjects who Withdraw from Investigational Product or Withdraw Consent During the DB or DB Follow-Up Periods

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

EODB Treatment/Early Termination (ET) procedures will be required whenever subjects discontinue treatment with investigational product in the DB/DB Follow-Up Period. The EODB Treatment/ET Visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product, but continues with regularly scheduled study visits, the ET Visit will be completed. The

actual investigational product discontinuation scenario (Table 8) will determine the sequence of the EODB treatment/ET Visits and procedures.

The following procedures will be performed at the EODB Treatment/ET visit:

- Assess AEs
- Monitor for potential myopathy
- Record concomitant medications
- Assess investigational product accountability and compliance
- 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted]
  - [redacted] (to be calculated by the Sponsor)
- [redacted]
- [redacted]
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)
- 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, and total and conjugated bilirubin
  - Thyroid hormones: free T3, free T4, and TSH
  - C4 and bile acids
  - [redacted]
  - [redacted]
- Urinalysis

- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential

When a subject ends her/his participation in the study (e.g., at a point between standard study visits) either due to ET (withdrawal of consent) or investigational product discontinuation, an ET Visit must be performed as near as possible to her/his 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 and EODB procedures in the eCRF.

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

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

DB = double-blind; EODB = end of double blind; ET = early termination; LTF = lost to follow-up; NA = not applicable.
[a] Refer to Table 3 (Schedule of Study Procedures During the DB Period) for all procedures and evaluations required at the EODB Treatment/ET Visit.

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

9.7.8. LTSE Period

All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period. Details of the move to the open-label phase of the LTSE Period will be provided in the SAP. The end of the trial is determined to be last patient last visit (LPLV) in the LTSE Period.

9.7.8.1. LTSE Day 1

LTSE Day 1 will begin when the last subject enrolled finishes the DB Period (Week 12). All other subjects that were held in the DB Follow-Up Period will then transition to LTSE. The following procedures will be performed as listed in Table 4:

- 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 within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect medical/surgical history
- Record concomitant medications
- Assess investigational product accountability and compliance
- Assess AEs
- Monitor for potential myopathy
- Record weight and BMI and WHR
- Perform physical examination
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Perform standard 12-lead ECG
- Calculations will be performed by the Sponsor or designee for the following:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted]
  - [redacted] (calculated by Sponsor)
- [redacted]
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)
- 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
  - [redacted]
  - C4 and bile acids
  - [redacted]
- Urinalysis

- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- Dispense/administer investigational products
- Remind subject to fast at least 8 hours prior to next dosing visit

9.7.8.2. LTSE Week 4, LTSE Week 12, LTSE Week 24, LTSE Week 36, LTSE Week 48, LTSE Week 60, LTSE Week 72, and LTSE Week 84

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 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 and BMI and WHR
- Perform physical examination (LTSE Week 12, LTSE Week 24, LTSE Week 36, LTSE Week 48, LTSE Week 60, LTSE Week 72, and LTSE Week 84 only)
- 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted]
  - [redacted] (to be calculated by Sponsor)
- [redacted]
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)
- Dispense/administer investigational products
- 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, and total and conjugated bilirubin
  - Thyroid Hormones (Free T3, free T4, and TSH; LTSE Week 4, LTSE Week 24, LTSE Week 48, and LTSE Week 72)
  - C4 and bile acids (LTSE Week 4, LTSE Week 24, LTSE Week 48, and LTSE Week 72)
  - [redacted]
  - [redacted]
- Urinalysis (LTSE Weeks 4, 12, 24, 48, 72)
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- [redacted] (at qualifying sites only)
- Remind subject to fast at least 8 hours prior to next dosing visit

9.7.8.3. LTSE Week 8 (Telephone Visit)

LTSE Week 8 will be conducted by telephone call. Subjects will be contacted for the following:

- Assess investigational product accountability and compliance
- Record concomitant medications
- Assess AEs
- Monitor for potential myopathy

9.7.8.4. LTSE Week 96

The following procedures will be performed at the LTSE Week 96 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 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 and 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted]
  - [redacted] (to be calculated by the Sponsor)
- [redacted]
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)
- Dispense/administer investigational products
- 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, and total and conjugated bilirubin
  - Thyroid Hormones (Free T3, free T4, and TSH)
  - C4 and bile acids
  - [redacted]
  - [redacted]
- Urinalysis
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- [redacted]

9.7.8.5. LTSE Week 108 and LTSE Week 120/EOS Visit

The following procedures will be performed at the LTSE Week 108 and 120/EOS Visits:

- 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 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 and BMI and WHR
- Perform physical examination
- Perform standard 12-lead ECG (LTSE Week 120/EOS only)
- 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:
  - [redacted]: to be calculated from serum chemistry and other parameters
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - [redacted] (to be calculated from serum chemistry and other parameters by the Sponsor)
  - [redacted] (to be calculated by the Sponsor)
- [redacted]
- [redacted] only applicable for subjects enrolling on or after protocol Version 4)
- Dispense/administer investigational products (LTSE Week 108 only)
- 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, and total and conjugated bilirubin
- Urinalysis (LTSE Week 120/EOS only)
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- [redacted]

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.

The solutions described in this section may not apply to the virtual site used in the study as most of the solutions have already been utilized by the virtual site.

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 into 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, CK 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: 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 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 biliary atresia (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 5 mg and 10 mg as well as matching OCA placebo tablets will be supplied as white, round, film-coated tablets throughout the study period. OCA tablets are 8-mm-diameter round tablets debossed with "INT" on 1 side and "3547" on the other side. The OCA 5 mg and 10 mg and matching placebo OCA tablets have the same tablet appearance. Each OCA tablet contains the following inactive ingredients: [redacted]

11.1.2. Bezafibrate

The investigational product for BZF 200-mg IR and matching placebo will be supplied as white, round, film-coated tablets in the throughout the study. The BZF 200-mg IR and matching placebo tablets are 10-mm diameter round tablets debossed with "G6" on 1 side and no markings on the other side. Each BZF 200-mg IR tablet contains the following inactive ingredients: [redacted] The matching placebo contains the following inactive ingredients: [redacted].

The investigational product for BZF 400-mg SR and matching placebo will be supplied as white, round, film-coated tablets. The BZF 400-mg SR and matching placebo tablets are 11-mm diameter round tablets debossed with "D9" on 1 side and no markings on the other side. Each BZF 400-mg SR tablet contains the following inactive ingredients: [redacted]. The matching placebo contains the following inactive ingredients: [redacted]

All investigational product will be manufactured according to Good Manufacturing Practices.

11.2. Investigational Product Packaging and Labeling

11.2.1. Double-Blind Period

All OCA 5 mg and matching placebo investigational product for the DB Period 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. The subject should take one tablet from the bottle daily to achieve the appropriate OCA treatment dose.

Active BZF and matching placebo investigational product will also be provided as tablets for oral administration for the DB Period 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 (200-mg IR and 400-mg SR) 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 BZF 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 (200 mg IR or 400 mg SR) or placebo. Kits will be dispensed to the subject according to the visit schedule in Table 3 and 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, one tablet from the OCA bottle and 2 tablets from the weekly blister wallet as described above.

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. Long-Term Safety Extension Period

Subjects will be held in the DB Follow-Up Period until the last subject finishes Week 12 of the DB Period. At which point, all subjects will transition to the LTSE Period of the study. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE Period. In the open-label phase of the LTSE Period, OCA 5 mg + BZF 400 mg SR investigational products will be dispensed in the same manner in dosing kits that contain 1 bottle of OCA 5 mg and weekly blister wallets that contain the BZF 400 mg SR dose as previously supplied during the DB period. Each subject should continue to take 3 tablets daily, one tablet from the OCA 5 mg bottle and 2 tablets (1 tablet BZF 400 mg SR, 1 tablet Placebo 200 mg IR) from the weekly BZF 400 mg SR blister wallet.

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 13 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 for the DB Period/DB Follow-Up Period and in Table 4 for the LTSE Period.

12.2. [redacted]

[redacted]

12.3. [redacted]

The [redacted] will be calculated from serum chemistry and other parameters by the Sponsor.

13. [redacted]

[redacted] will be performed according to the schedule presented in Table 3 for the DB/DB Follow-Up Period and in Table 4 for the LTSE Period.

[redacted] will be based on laboratory assessment [redacted] and will be calculated by the Sponsor.

[redacted]. The test can be performed by staff who are trained in the use and data interpretation of the diagnostic test. Blood samples for measurement of [redacted] will be performed according to the schedule listed in Table 3 and Table 4.

The [redacted] will be collected and assessed at the indicated visits.

14. CLINICAL PHARMACOLOGY ASSESSMENTS

Subjects who receive at least 1 dose of OCA and BZF and have bioanalytical concentration data available will be included in the PK analysis. Subjects with at least 1 valid PD assessment after dosing will be included in the combined PK/PD analyses. Any missing samples will be removed from the analyses, and no imputation will be performed.

14.1. PK Blood Sampling

[redacted]

The acceptable windows for sample collection are shown in Table 9.

[redacted]

14.2. [redacted]

[redacted]

At Screening, a separate ICF will be used to obtain subjects' consent for the collection of the [redacted]

Blood will be collected at on Day 1 from each subject who consented to have a blood sample collected for [redacted].

[redacted] will be analyzed when deemed necessary and/or will be stored at the repository facility after the completion of clinical study report.

The [redacted] will be provided as part of the final clinical study report or will be reported in a separate document if deemed appropriate.

14.3. [redacted]

[redacted]

14.4. Bioanalysis

Plasma concentrations of OCA and its [redacted] will be determined using validated liquid-chromatography mass spectrometry/mass spectrometry method.

BZF concentrations will be determined using appropriate validated bioanalytical methods. [redacted] may also be quantitated in this study if deemed appropriate.

[redacted]

[redacted]

14.5. [redacted]

[redacted] will be collected at the indicated visits and assessed using appropriate validated or qualified methods.

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/DB Follow-Up Periods and the LTSE Period.

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-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. 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 medicinal 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 10. 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 10: Relationship of Adverse Events to Treatment Regimen

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

15.1.3. 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 11, must be entered on the AE CRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 11: Severity of Adverse Events

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

15.1.3.1. 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 12. In order to assess the potential improvement in pruritus with treatment, baseline pruritus presence (yes/no) and severity (as shown in Table 12) will be determined.

Table 12: 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 problematic 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 ≥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. A drug holiday should be resolved before a subject transitions into the LTSE Period.

- Subjects taking BAS (including cholestyramine and its derivatives, colestipol, colesevelam, or other BAS) or aluminum hydroxide- or smectite-containing antacids should refrain from using these drugs for the management of pruritus during the trial. The use of BAS may alter the interpretation of the effects of BZF on pruritus.
- 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.

15.1.4. Reporting of Adverse Events and Serious Adverse Events

15.1.4.1. Reporting of Adverse Events

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

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.

15.1.4.2. Reporting of Serious Adverse Events

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

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:

- Email 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 products. 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.

15.1.5. Additional Investigator Responsibilities for SAEs

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

The Investigator and supporting personnel responsible for subject care should discuss 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 15.1.4.2.

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 15.1.4.2.

If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (i.e., within 24 hours) by following the instructions provided in Section 15.1.4.

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

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 CRF 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 15.1.4 must also be followed.

15.2. Other Safety Parameters

15.2.1. [redacted]

[redacted]

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. 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).

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 patients 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. The score uses 5 clinical measures of liver disease (total bilirubin, serum albumin, PT, ascites, and hepatic encephalopathy), each scored from 1 to 3, with 3 indicating most severe (see Table 7).

15.2.5. Vital Signs

Vital signs, height, and weight will be assessed at the visits as specified in Table 3. Vital signs taken will include 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 at the time points indicated in Table 3 and Table 4. ECGs will be recorded using the site's standard ECG equipment. Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the Investigator based on GCP.

All ECGs should be collected after at least 5 minutes of supine rest and prior to blood sample collection. Safety ECGs will be obtained using a 12-lead digital ECG recorder. The ECG will

include all 12-standard leads and will be recorded at a paper speed of 25 mm/sec. Standard ECG parameters will be measured, including heart rate (HR), RR, PR, QT, QTc intervals, and QRS duration. 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 CS, or abnormal and CS. Any CS abnormality on ECGs recorded after dosing 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.

The investigative site must retain a copy of all 12-lead ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the subject's initials, Subject ID number, date, and time.

15.2.7. 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 (DB/DB Follow-Up Periods) and Table 4 (LTSE period).

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 test (serum quantitative β-hCG) 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 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, [redacted] will be calculated based on demographic, examination, and clinical laboratory values as described in the SAP.

[redacted] will be calculated from serum chemistry and other parameters collected at the same visit with scores recorded on the eCRF.

[redacted]

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

The list of laboratory analytes to be tested is shown in Table 13.

Table 13: List of Laboratory Scores and Analytes

Laboratory Assessment	Scores and Analytes[a]
Serum chemistry	Albumin, ALP, BUN, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), 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
[redacted]	
Thyroid function tests	Free T3, free T4, and TSH
Virology	HBsAg, HCV
Pregnancy test (female subjects of childbearing potential)[b]	β-hCG
[redacted]	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted]; aPTT = partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; BZF = bezafibrate; [redacted]; CK=creatine kinase; CP = child-pugh score; eGFR = estimated glomerular filtration rate; [redacted] GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; INR = international

normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; [redacted]; OCA = obeticholic acid; [redacted] PT = prothrombin time; T3 = triiodothyronine; T4 = thyroxine; [redacted]; TG = triglycerides; TSH = thyroid-stimulating hormone; [redacted]; VLDL = very-low-density lipoprotein

[a] Overlapping analytes will be analyzed only once.

[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 test (serum quantitative β-hCG) 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] For subjects who have consented.

15.2.8. Health-Related Quality of Life

See Section 12.2 for questionnaires to be used.

15.3. Hepatic Safety Adjudication

All potential events of hepatic injury that occur after administration of the first dose of investigational products during the double-blind and LTSE Period will be adjudicated 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, 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

A SAP will be prepared and finalized before study database lock and unblinding of the study, which will provide details about the specific planned analyses. The SAP will be prepared as soon as planning for the statistical methods section of the protocol is initiated. The first draft will be completed before the finalization of the study's case report forms to ensure alignment of data collection procedures with the SAP. 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 Intent-to-Treat (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 BZF and/or OCA during the LTSE Period.

16.2. Determination of Sample Size

[redacted]

is 58. Assuming the change from baseline in ALP with BZF treatment is -146 U/L, a sample size of 18 subjects per arm will provide 80% power to detect a treatment difference of 54 between the BZF and BZF+OCA arms at two-sided alpha of 0.05 with the pooled standard deviation of 58.

16.3. Primary Efficacy Analysis

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

The primary efficacy endpoint is the change in ALP from baseline to Week 12 in the DB Period. For the primary efficacy analysis, the subjects with baseline and at least one post-baseline ALP will be included in the analysis.

[redacted]

[redacted]

In addition, a sensitivity analysis using mITT Population will be performed on the primary efficacy endpoint, where data collected after the intercurrent events will not be included in the analysis. This provides the evaluation of efficacy effect regardless of treatment adherence.

16.4. Secondary and Additional Efficacy Analyses

The ITT Population will be the primary population used for the secondary and additional efficacy analyses. All randomized subjects will be included in the secondary and additional efficacy analyses.

The secondary endpoints include:

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

The additional efficacy endpoints include:

- Percent change from baseline of ALP at Week 12
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]



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

16.5.



16.6. LTSE Analyses

Similar analyses to that described for the DB Period will be conducted for the LTSE Period using the DB baseline value with the exception of PK, which will not be performed during the LTSE period. Analyses based on the DB baseline will be performed using randomized treatment groups in the DB Period.

16.7. Interim Analysis

There will be a planned interim analysis performed when at least 40 subjects complete the Week 12 visit in accordance with the SAP and DMC Charter. The primary endpoint for this planned interim analysis will be the change from baseline in ALP at Week 12. The SAP will specify the methods for the interim analysis as well as additional details on the conductance. The interim analysis will be conducted by a Sponsor sub-team that will not be part of the study level activities. The data access plan (DAP) will specify the make-up of the Sponsor sub-team and the appropriate data fire-walls to ensure data-integrity. The DMC will review the interim criterion for safety data and other relevant information to determine whether to continue the study.

The findings of the interim analysis will be presented to both the DMC and a Sponsor sub-team. After the interim analysis is completed, the Sponsor sub-team will review safety, efficacy, and PK data for the purpose of selecting a fixed-dose combination for a future marketed product and for regulatory interaction. With the exception of a small Sponsor sub-team who will know the results of the interim analysis, blinding of all operational site staff and the Sponsor will be maintained until the database has been locked for the DB Period. The Sponsor sub-team will be excluded from study conductance and appropriate firewalls will be established for the remainder of the DB Period (as described in the DAP). When all subjects have completed the DB Period, the study will convert to an LTSE. Details of the unblinding and data access plan will be provided in separate documents.

The efficacy measures for the interim analysis include:

- Primary Endpoint: The change in ALP from baseline to Week 12 in the DB Period in the mITT Population
- Secondary Endpoints:
  - The ALP response rates of ≥10%, ≥20%, ≥30%, and ≥40% reduction from baseline at Week 12 and the normalization rates of ALP at Week 12 in the ITT Population
  - Changes from baseline to Week 12 in GGT, ALT, AST, total and conjugated bilirubin, and a lipid panel in the ITT Population
- Additional Endpoint:
  - [redacted].

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

Those endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.

Additional Rolling Interim Analysis

The Sponsor will have the option to perform an additional unblinded rolling analysis of efficacy, PK, and safety data throughout the DB Period. Details of the unblinding and Data Access Plan, including Sponsor staff that will be unblinded, will be provided. All Principal Investigators (PIs), site staff, and subjects will remain blinded throughout 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 (including a lipid panel), and treatment discontinuations, will be compared across all treatment groups during the DB Period.

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. Clinical Laboratory Evaluations

Laboratory parameters and vital signs will be summarized 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 designee will perform data review on a regular basis throughout the conduct of a study in accordance to the 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 electronic data capture (EDC) system and completion of the electronic Case Report Forms (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.

16.11. Data Monitoring Committee

The Data Monitoring Committee (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 period 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 general DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the FDA debarment list will not be offered membership; financial disclosure will be required. Conflicts of interest will be assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The DMC will meet approximately quarterly at scheduled meetings, and ad hoc meetings will be convened, as appropriate, to review safety data. 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. Details of this committee's responsibilities and processes can be found in the DMC charter.

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 fake 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) are reviewed by the DMC, in addition to a cumulative list of all SAEs.

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

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

Data flow, access, process, and disclosure will be described in a data access plan.

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 participants. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/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 of the clinical studies that it sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

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

- Clinical Trial Registries (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.

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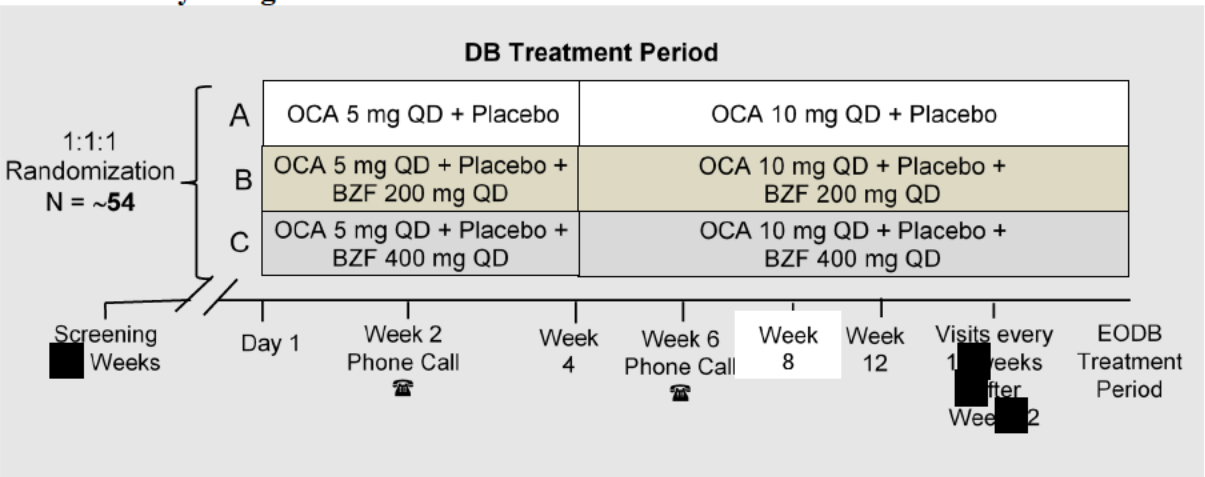
APPENDIX A. STUDY 747-213 PROTOCOL VERSION 2

747-213 Version 2 Treatment Assignment

Treatment	DB Treatment Morning Dose Regimen
Treatment A: OCA 5 mg→10 mg QD	**1 OCA 5 mg tablet (Weeks 0 to 4)** **1 OCA 10 mg tablet (Week 4 to end of DB treatment)** 1 placebo BZF 200 mg IR tablet 1 placebo BZF 400 mg SR tablet
Treatment B: OCA 5 mg→10 mg QD + BZF 200 mg IR QD	**1 OCA 5 mg tablet (Weeks 0 to 4)** **1 OCA 10 mg tablet (Week 4 to end of DB treatment)** **1 BZF 200 mg IR tablet** 1 placebo BZF 400 mg SR tablet
Treatment C: OCA 5 mg→10 mg QD + BZF 400 mg SR QD	**1 OCA 5 mg tablet (Weeks 0 to 4)** **1 OCA 10 mg tablet (Week 4 to end of DB treatment)** 1 placebo BZF 200 mg IR tablet **1 BZF 400 mg SR tablet**

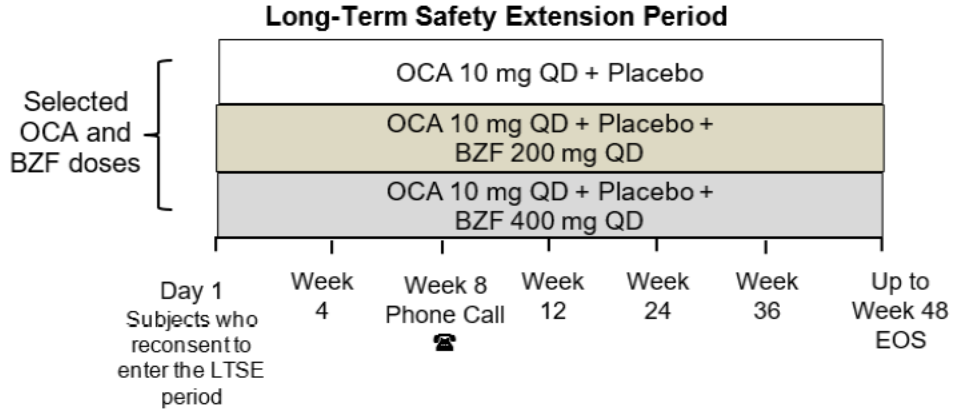
BZF = bezafibrate; DB = double-blind; IR = immediate release; OCA = obeticholic acid; QD = once daily; SR = sustained release.
Active treatments are in bold text.

747-213 Study Design for Double-Blind and LTSE Periods



BZF = bezafibrate; DB = double-blind; EODB = end of DB; LTSE = long-term safety extension; OCA = obeticholic acid; QD = once daily; UDCA = ursodeoxycholic acid.
Note: Subjects taking UDCA at the time of enrollment will remain on their stable dose of UDCA during the study.
Note: DB dose will continue into the LTSE period once subject has completed the 12-wk DB component of the trial.

Study Design Diagram of the Long-Term Safety Extension Period:



BZF = bezafibrate; EOS = end of study/end of LTSE Period; LTSE = long-term safety extension; OCA = obeticholic acid; QD = once daily; UDCA = ursodeoxycholic acid.

APPENDIX B. 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 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 in patients with PBC
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 C. SUMMARY OF CHANGES: PROTOCOL 747-213 VERSION 7.0 (DATED 08 OCT 2024)

The following is a summary of key changes made to Protocol 747-213 Version 7.0:

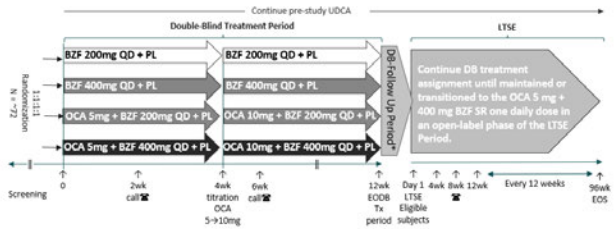
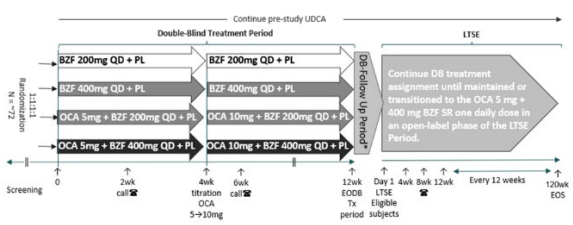
- Updated the title page with current EU CT number and confidential statement
- Added a short title of the study and ethical conduct of study to the synopsis
- Inclusion #5: added clarifying language and updated the definition of sexual abstinence

Changes to the Long-Term Safety Extension (LTSE) Phase are as follows:

- Extended the total duration of the LTSE Period from 96 weeks to 120 weeks and updated the schedule of study procedures to add LTSE visits and assessments on Week 108 and 120 visits.

The text deleted from Protocol Version 6.0 is crossed out and revised text in Version 7.0 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 7.0 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 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
Title Page	~~EudraCT~~ Number: ~~2018-002575-17~~	**EU CT** Number: **2024-513762-18**	Per EU guidelines, the application number should be referred to as EU CT. Updated the EU CT number.
Title Page	~~The information contained herein is the property of Intercept Pharmaceuticals, Inc., and may not be reproduced,~~ published~~, or disclosed to others~~ without written ~~authorization of~~ Intercept Pharmaceuticals, Inc.	**This document contains confidential information, which should not be copied, referred to, released or** published without written **approval from** Intercept Pharmaceuticals, Inc.**, a subsidiary of Alfasigma S.p.A.**	Updated to include Alfasigma S.p.A.
Synopsis	*New text*	**Short Title of Study:** **A Phase 2 Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid Administered in Combination with Bezafibrate in Subjects with Primary Biliary Cholangitis**	Added to comply with regulatory guidance.
Synopsis	Estimated date last subject completed: ~~Jul 2024~~	Estimated date last subject completed: **Oct 2025**	Extended LTSE Period to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites.

Section	Original Text (Version 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
Synopsis Additional Objectives 6.3 Additional Objectives	[redacted]		
Synopsis Methodology 7.1.1 Methodology	Long-Term Safety Extension (LTSE) Period (up to ~~96~~ Weeks): All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE. All site staff will maintain study blind until the study is moved to the open-label phase of the LTSE Period. Safety and laboratory assessments will be evaluated at clinic visits once every 12 weeks and up to Week ~~96~~.	Long-Term Safety Extension (LTSE) Period (up to **120** Weeks): All subjects will transition to the LTSE Period when the last subject completes Week 12 of the DB Period. Subjects will continue the original treatment assignment allocated during the DB Period until maintained or transitioned to the OCA 5 mg + 400 mg BZF SR once daily dose in an open-label phase of the LTSE. All site staff will maintain study blind until the study is moved to the open-label phase of the LTSE Period. Safety and laboratory assessments will be evaluated at clinic visits once every 12 weeks and up to Week **120**.	Extended LTSE Period to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites.
Synopsis Methodology 7.1.1, Methodology Figure 1			Extended LTSE Period to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites.

Section	Original Text (Version 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
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. … • 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 Period.	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. **Highly effective methods of contraception are as follows:** … • Sexual abstinence, as a form of highly effective contraception **if in line with the preferred and usual lifestyle of the subject**, 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 Period.	Added clarifying language to align with other study programs. Clarified language on sexual abstinence and effective methods of contraception.
Synopsis Duration of Treatment 7.1.3 Study Duration	The duration of treatment per subject will be a minimum of approximately 108 weeks, which includes a 12-week DB Period, followed by ~~96~~ weeks of treatment during the LTSE Period.	The duration of treatment per subject will be a minimum of approximately 108 weeks, which includes a 12-week DB Period, followed by **120** weeks of treatment during the LTSE Period.	Extended LTSE Period to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites.

Section	Original Text (Version 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
Synopsis	*New text*	**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 International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements and the Sponsor's policies.**	Added to comply with regulatory guidance.
7.1.2 Schedule of Study Procedures, Table 4	*New Columns* … Note: Week ~~96~~ is the last visit in the LTSE Period. Week ~~96~~ is the EOS. If a subject discontinues treatment or discontinues the study before Week ~~96~~, they should come in for the EOS Visit which will be their final visit. Week ~~96~~ and EOS have the same assessments required.	*Week 96 Visit updated from EOS to regular study visit. Visit Columns added for: LTSE Weeks 108 and 120 (EOS)* … Note: Week **120** is the last visit in the LTSE Period. Week **120** is the EOS. If a subject discontinues treatment or discontinues the study before Week **120**, they should come in for the EOS Visit which will be their final visit. Week **120** and EOS have the same assessments required.	Extended LTSE Period to ensure patients could continue treatment until the Phase 2/3 LTSE protocol is initiated at study sites.
9.7.8.4 LTSE Week 96	9.7.8.4 LTSE Week 96~~/EOS Visit~~ The following procedures will be performed at the LTSE Week 96~~/EOS Visit~~: … • ~~Perform standard 12-lead ECG~~ *New text*	9.7.8.4 LTSE Week 96 The following procedures will be performed at the LTSE Week 96 Visit: **…** *Removed text* • **Dispense/administer investigational products**	Updated LTSE EOS visit to align with extension of the LTSE Period from 96 weeks to 120 weeks. Removed ECG from Week 96 since it will be performed at EOS Week 120.

Section	Original Text (Version 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
			Extended LTSE Period and investigational product will be provided at Week 96.
9.7.8.5 LTSE Week 108 and LTSE Week 120/EOS Visit	*New text*	**9.7.8.5. LTSE Week 108 and 120 Visits/EOS Visit** **The following procedures will be performed at the LTSE Week 108 and 120/EOS Visits:** • **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 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 and BMI and WHR** • **Perform physical examination** • **Perform standard 12-lead ECG (LTSE Week 120/EOS only)** • **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:** - [redacted] **to be calculated from serum chemistry and other parameters**	Extended LTSE Period and added procedures to be conducted at the additional LTSE visits.

Section	Original Text (Version 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
		- **CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.** - [redacted] **(to be calculated from serum chemistry and other parameters by the Sponsor)** - [redacted] **(to be calculated by the Sponsor)** • [redacted] • [redacted] • **Dispense/administer investigational products (LTSE Week 108 only)** • **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, and total and conjugated bilirubin** • **Urinalysis (LTSE Week 120/EOS only)** • **Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential** • [redacted]	

Section	Original Text (Version 6.0, 31 Oct 2023)	Revised Text (Version 7.0, 08 Oct 2024)	Key Change Reasons/ Justification for Change
[redacted]			