Clinical Study Protocol 977-311

OBETICHOLIC ACID (OCA) AND BEZAFIBRATE (BZF)

A Phase 3, Open-Label, Long-Term Safety Extension Study Evaluating the Safety and Tolerability of the Fixed-Dose Combination of Obeticholic Acid and Bezafibrate in Subjects with Primary Biliary Cholangitis

Version 2: 18 November 2024

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Sponsor

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

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Electronically signed by: [redacted]
Reason: I have reviewed this document
Date: Nov 18, 2024 14:32 PST

18-Nov-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 (IBs) for obeticholic acid (OCA) and the fixed-dose combination (FDC) (OCA and bezafibrate [BZF]) and this Protocol 977-311. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA/BZF FDC to selected subjects according to this protocol.

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

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

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 977-311 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

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

_____

Investigator's Name (Printed)

_____ _____

Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Products:

Obeticholic acid (OCA) and bezafibrate (BZF) in fixed-dose combination (FDC)

Name of Active Ingredient:

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

Title of Study:

A Phase 3, Open-Label, Long-Term Safety Extension Study Evaluating the Safety and Tolerability of the Fixed-Dose Combination of Obeticholic Acid and Bezafibrate in Subjects with Primary Biliary Cholangitis

Investigators and/or Study Center(s):

Approximately 60 investigational sites, globally

Studied Period:

Actual date first subject enrolled: July 2024

Estimated date last subject completed: Q2 2029

Phase of Development: Phase 3

Objectives:

Primary Objective:

The primary objective is to assess the long-term safety and tolerability of the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg sustained release [SR]) in subjects with primary biliary cholangitis (PBC).

Efficacy Objectives:

To assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following:

- Biochemical disease markers, including ALP, GGT, ALT, AST, and total and conjugated bilirubin
- ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline
- Noninvasive assessments of liver fibrosis (transient elastography [TE], enhanced liver fibrosis [ELF] score)
- Disease severity scores (GLOBE, UK-PBC, and model of end-stage liver disease [MELD])

Exploratory Objectives:

To assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following:

[redacted]

[redacted]

- MELD score ≥15

[redacted]

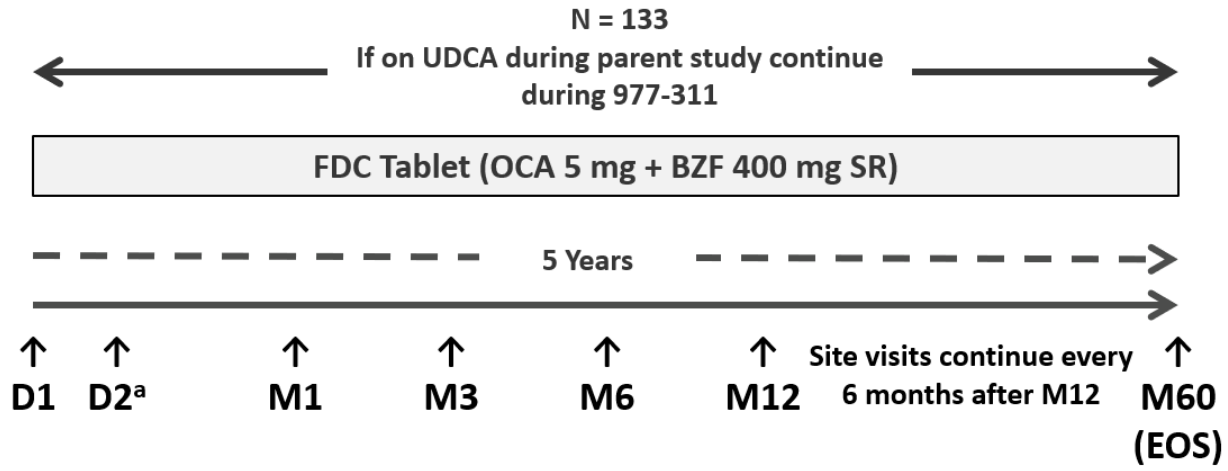
Methodology:

Overview: This Phase 3, open-label, long-term safety extension (LTSE) study will evaluate the safety, tolerability, and efficacy of the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) in approximately 133 subjects with PBC for up to 60 months (5 years). Subjects from Study 747-213 or Study 747-214 will transition into Study 977-311 once Study 977-311 is active at their respective sites. The time subjects have spent in the LTSE phases in their respective studies, 747-213 or 747-214, will not count toward the 60 months in Study 977-311. Eligible subjects from other Sponsor studies may also transition to Study 977-311.

All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits) starting on Day 2. All subjects should continue their pre-study dose of ursodeoxycholic acid (UDCA) throughout study participation.

After the Day 1, Day 2, Month 1, Month 3, Month 6, and Month 12 visits, subsequent in-clinic study visits will occur every 6 months for the assessment of safety, tolerability, efficacy, PK, and PD.

Study Design Diagram



BZF=bezafibrate; D=day; EOS=end of study; FDC=fixed-dose combination; IP=investigational product; LTSE=long-term safety extension; M=month; OCA=obeticholic acid; SR=sustained release; UDCA=ursodeoxycholic acid

Notes: Subjects taking UDCA at the time of enrollment will remain on their stable dose of UDCA during the study. Subjects will be re-consented.

Subjects in either Study 747-213 or Study 747-214 may already be in LTSE. The time subjects spent in LTSE on either study will not be carried over into this study, 977-311. Subjects will spend a total of 60 months (5 years) in Study 977-311.

[a] The Day 2 Visit can be either a virtual or onsite visit. It will be scheduled on Day 2 to Day 7 of the study depending on when laboratory results are available and reviewed. Subjects can elect to pickup IP onsite (onsite Day 2 visit) or have it shipped directly to them (virtual Day 2 visit). For subjects that have IP shipped, the Day 2 virtual visit should be scheduled once the subject receives IP.

Number of Subjects (Planned):

Approximately 133 subjects

Diagnosis and Main Criteria for Inclusion:

1. All subjects with PBC who participated and are actively taking investigational product in Study 747-213 or Study 747-214 (or other Sponsor studies) are eligible to enroll in this study (977-311).
   - Subjects on a drug holiday within the previous 60 days due to unresolved treatment emergent adverse events (TEAEs) or serious adverse events (SAEs) in the parent study should discuss eligibility for rolling over to this study with the Sponsor Medical Monitor.
2. 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 at least 30 days after the last dose of investigational product. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from exposure to investigational medicinal products. Highly effective methods of contraception are as follows:
   - Intrauterine device
     - Intrauterine device
     - Intrauterine hormone-releasing system
   - 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 of their parent study.
- 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 of their parent study.
- 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 30 days 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.

3. Male subjects who are sexually active with female partners of childbearing potential must agree to use a condom with spermicide and to use (or have their partner use) 1 other approved method of highly effective contraception from the initiation of the study and until at least 90 days after the last dose of investigational product as listed in Inclusion Criterion #2.
4. Male patients must refrain from sperm donation from the initiation of the study and until at least 90 days after the last dose of investigational product.
5. Must provide written informed consent and agree to comply with the study protocol.

Key Exclusion Criteria:

1. Any history or presence in the last 30 days, before rolling over to this study, of other concomitant liver diseases, including any of the following:
   - Hepatitis C virus (HCV) infection with positive RNA
   - 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 and Sponsor 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-autoimmune hepatitis (AIH) overlap
   - Metabolic dysfunction-associated steatohepatitis (MASH)
   - Gilbert's Syndrome (due to interpretability of bilirubin levels)
   - Rare liver conditions such as Wilson's disease, hemochromatosis, alpha-one anti-trypsin deficiency, or other conditions identified by the Principal Investigator
2. Clinical complications of PBC including:
   - Prior liver transplantation
3. Any history or presence in the last 30 days, before rolling over to this study, of any one of the following decompensating events:
   - Child-Pugh (CP) Score ≥7

- Clinical evidence of decompensated liver disease or evidence of portal hypertension, including but not limited to:
  - Varices (including a history of esophageal varix ligation or asymptomatic esophageal varices by endoscopy)
  - 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 >ULN
  - International normalized ratio (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 II) or serum creatinine >1.5 mg/dL (135 µmol/L) or estimated glomerular filtration rate (eGFR) <60 mL/min from the last lab assessment/visit in parent study, before transitioning to Study 977-311
- Portopulmonary hypertension
- Hepatopulmonary syndrome

4. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) or that 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. Evidence or history of cholelithiasis or choledocholithiasis unless documented cholecystectomy. Gallbladder polyps if >5 mm in diameter
7. History of chronic pancreatitis or recurrent acute pancreatitis – defined as at least 2 episodes of acute pancreatitis, with symptoms resolving between each episode
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 the last visit in parent study, before transitioning to Study 977-311
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, QT interval of the electrocardiogram (QT) or QT interval of the electrocardiogram corrected (QTc) interval of >450 milliseconds for males and >470 milliseconds for females
13. Severe pruritus or required systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin) within 2 months of Day 1 of Study 977-311. Subjects who plan to use or will use BAS during the study will not be eligible.

14. History of known or suspected clinically significant (CS) hypersensitivity to OCA, BZF, or other fibrates or any of their components
15. Known photoallergic or phototoxic reactions to fibrates
16. If female, known pregnancy, a positive urine pregnancy test (confirmed by a positive quantitative serum pregnancy test), or current lactation at the last visit in parent study, before transitioning to Study 977-311
17. Other CS medical conditions that are not well controlled or for which medication needs are anticipated to change during the study (e.g., Type 2 diabetes mellitus, hypothyroidism, nephritic or nephrotic syndrome, dysproteinemia, obstructive biliary disease, dyslipidemia), and/or up to the discretion of the Principal Investigator
18. Treatment with the following medications 30 days before Day 1 of Study 977-311, or plans to use these medications during the study: azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, rifampicin, statins, budesonide and other systemic corticosteroids (short-term use up to 2 weeks is permitted), monoamine oxidase inhibitors (MAOIs), and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazid, and nitrofurantoin)
19. Treatment with the following medications within 12 months before Day 1 of Study 977-311, or plans to use these medications during the study: antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
20. Participation in a study of another investigational medicine or device within 30 days before Day 1 of Study 977-311 (except for Study 747-213, Study 747-214, or other eligible Sponsor study)
21. History of or ongoing alcohol or drug abuse within 1 year before Day 1 of Study 977-311. Subjects with moderate alcohol use within 3 months prior to the last visit in parent study, before transitioning to Study 977-311, 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), or 1.5 ounces of 80 proof (40% alcohol)
22. History of noncompliance with medical regimens, or is considered by the Principal Investigator not able to meet the requirements as specified in the protocol from Day 1 throughout the duration of the study
23. Blood or plasma donation within 30 days before Day 1
24. Mental illness or other condition which may impair decision making, such that the validity of informed consent or ability to be compliant with the study is uncertain
25. A creatine kinase (CK) value on Day 1 of Study 977-311 ≥5x ULN or any abnormal laboratory value that is considered CS in the opinion of the Principal Investigator and Sponsor at the last visit in parent study, before transitioning to Study 977-311
26. Known or suspected nephrotic syndrome in the last 30 days, before rolling over to this study, based on the following diagnostic criteria (both Type 1 and Type 2):
    - Proteinuria, spot urine protein: albumin/creatinine ratio (ACR) of >300 mg/mmol (subjects with normal renal function and ACR values analyzed to be below the lower limits of detection are permitted)
    - Serum albumin <25 g/L
    - Clinical evidence of peripheral edema
    - Severe hyperlipidemia (total cholesterol above >10 mmol/L)

Hepatic and Renal Event Adjudication:

All events of potential hepatic injury, suspected liver-related clinical outcomes, and potential renal injury that occur after administration of the first dose of investigational product will be reviewed and adjudicated by independent and blinded adjudication committees, depending on event type.

Each adjudication committee has a charter that documents the reporting of events by the study site, definition of the potential events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

Specific details of the events that will be adjudicated are described in the respective adjudication charters. 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, Data Monitoring Committee (DMC) members, or consultants. Any candidate found to have a conflict or whose name is listed on the Food and Drug Administration (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, Good Clinical Practice (GCP), and all other applicable regulatory requirements, including the archiving of essential documents.

Investigational Products, Dosage, and Mode of Administration:

The single FDC tablet must be swallowed whole and not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout the study period. Subjects are requested to take medication in the morning. Specific instructions for dosing will be provided for PK assessment days.

- FDC tablet (OCA 5 mg + BZF 400 mg SR), once daily

The FDC tablet will be dispensed in a bottle. Each subject should take 1 tablet daily. The FDC tablet will be provided for use only in this study and is not to be used for any other purpose. The Principal Investigator or designee will maintain a full record of investigational product accountability, including records of individual subject dispensing and final return or disposition (as directed by the Sponsor).

Duration of Treatment:

The total duration of Study 977-311 per subject will be a maximum of 60 months from day of study entry. The end of study is defined as the date of the last visit of the last subject.

Statistical Methods:

Analysis Populations:

LTSE Population: The LTSE Population will include all subjects who receive at least 1 dose of the FDC tablet in Study 977-311.

Pharmacokinetic Population: The PK Population will include all subjects in LTSE Population who receive the FDC tablet in Study 977-311 and have a PK sample(s) without any major protocol deviations that could potentially affect plasma exposure.

Pharmacodynamic Population: The PD Population will include all subjects with a baseline assessment and at least 1 on-treatment assessment without any major protocol deviations that could potentially affect results.

Safety Analyses:

The LTSE Population will be the primary population used for safety analyses.

Safety data, including SAEs, TEAEs, physical examinations, electrocardiograms (ECGs), vital signs, clinical laboratory assessments, and treatment discontinuations, will be assessed.

The incidence of TEAEs and SAEs will be tabulated by system organ class, preferred term, and severity.

Laboratory parameters and vital signs will be summarized (including Hy's law) using descriptive statistics at baseline (defined as the last assessment performed before the first dose of investigational product in Study 977-311) and at each scheduled post-baseline visit in Study 977-311. The change from baseline will also be summarized. ECGs will be summarized using frequency at each visit. The shift from baseline will also be summarized.

Analyses of Efficacy and Exploratory Endpoints:

The LTSE Population will be the population used for the efficacy and exploratory analyses. Baseline is defined as the last assessment performed before the first dose of investigational product in Study 977-311, unless otherwise specified.

The efficacy endpoint at post-baseline site visits includes:

- Response rate of ≥40% reduction from baseline and normalization rates of ALP
- Normalization rates of GGT, ALT, AST, total and conjugated bilirubin
- Change from baseline in GGT, ALT, ALP, AST, and total and conjugated bilirubin
- Percentage of subjects with ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline
- Change from baseline in noninvasive markers of liver fibrosis, including liver stiffness measured by TE and ELF score
- Change from baseline in the GLOBE, UK-PBC, and MELD scores

The exploratory endpoints at post-baseline site visits include:

[redacted]

  - MELD score ≥15

[redacted]

[redacted]

- Time to first occurrence of each individual component of the composite event endpoint.

All continuous and categorical efficacy and exploratory endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.

Additional details regarding the planned analyses, methods, and outputs for the study will be included in the Statistical Analysis Plan (SAP).

PK, PD and PK/PD Analyses

The PK Population will be the primary population used for the PK analyses. The PD population will be the primary population for PD analyses. For PK/PD analyses, subjects in both the PK population and the PD population for the PD endpoint of interest will be included in the analysis. [redacted] will be summarized using descriptive statistics at each scheduled post-baseline visit. Change from baseline and percent change from baseline in [redacted] will be calculated by timepoint and reported in individual listings and descriptive summary tables. PK/PD analyses may consist of scatter plots with correlation analysis and additional analyses if warranted by the data.

Sample Size Determination

This is an estimation study with no formal hypothesis to be tested. Therefore, sample size is strictly based on number of subjects being captured from studies 747-213 and 747-214, or other Sponsor studies. The sample size in this study is not calculated based on statistical consideration.

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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
AE	adverse event
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-hCG	beta human chorionic gonadotropin
BAS	bile acid sequestrants
BMI	body mass index
BZF	bezafibrate
[redacted]	
CCDS	Company Core Data Sheet
CI	confidence interval
CK	creatine kinase
CrCl	creatinine clearance
C_{max}	maximum plasma concentration
CP	Child-Pugh
CRA	Clinical Research Associate
CS	clinically significant
CSR	clinical study report
CYP	cytochrome P
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DMP	Data Management Plan
DNA	deoxyribonucleic acid

Abbreviation or Specialist Term	Explanation
eAB	e-antibody
eAg	e-antigen
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
FDC	fixed-dose combination
FIS	Fatigue Impact Scale
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCP	healthcare provider
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDLc	high-density lipoprotein cholesterol
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
[redacted]	
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
INR	international normalized ratio
IP	investigational product
IR	immediate release
IRB	Institutional Review Board
ISF	investigator site file
KM	Kaplan-Meier
LDL	low-density lipoprotein
LS	least square
LSM	liver stiffness measurement
LTSE	long-term safety extension
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary of Regulatory Activities
MELD	model of end-stage liver disease
MRS	Mayo Risk Score
MASH	metabolic dysfunction-associated steatohepatitis
[redacted]	
OCA	obeticholic acid
PBC	primary biliary cholangitis
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PMN	polymorph leukocyte
PPAR	pan-peroxisome proliferator-activated receptor
[redacted]	
PSC	primary sclerosing cholangitis
PT	prothrombin time
QOL	Quality of Life
QT	QT interval of the electrocardiogram
QTc	QT interval of the electrocardiogram corrected
RNA	ribonucleic acid

Abbreviation or Specialist Term	Explanation
SAE	serious adverse event
sAB	surface antibody
sAg	surface antigen
SAP	Statistical Analysis Plan
SAR	suspected adverse reaction
SD	standard deviation
SR	sustained release
SSC	secondary sclerosing cholangitis
SUSAR	suspected unexpected serious adverse reaction
TB	total bilirubin
TE	transient elastography
TEAE	treatment-emergent adverse event
TT	triple therapies
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
USPI	United States Prescribing Information
US	United States
VAS	visual analog scale
WHR	waist-to-hip ratio

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, 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 chenodeoxycholic acid, 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 visual analog scale (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 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 4 studies include a Phase 1 study in healthy subjects (Study 747-123), a Phase 2 study (Study 747-213) in subjects with PBC that is being conducted globally (not including the US), a Phase 2 study (Study 747-214) being conducted globally (including the US) 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, and a Phase 1 absorption, metabolism, and excretion study of BZF (Study 977-113) in healthy subjects.

Study 747-123 is a completed, Phase 1, randomized, controlled study evaluating single-dose escalation of BZF 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 enrolled 132 healthy subjects.

Study 747-213 is an ongoing, Phase 2, double-blind, randomized, parallel group study evaluating the efficacy, safety and tolerability of OCA administered in combination with BZF in subjects with PBC who had an inadequate response or who were unable to tolerate UDCA. This study

has been fully enrolled (75 subjects), with a long-term safety extension (LTSE) currently ongoing. Subjects from Study 747-213 will transition into Study 977-311 once the study is active at their respective sites.

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 LTSE Period (up to 48 Weeks) being conducted in the US and non-US countries. 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 (72 subjects), with an LTSE currently ongoing. Subjects from Study 747-214 will transition into Study 977-311 once the study is active at their respective sites.

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 [redacted] mg of [14C]-bezafibrate capsule(s) containing approximately [redacted] µCi, followed up by a 14-day inpatient evaluation period.

5.4.1. Obeticholic Acid

As of 26 May 2024, approximately 4851 subjects have received ≥1 dose of 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 multiple 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 Company Core Data Sheet (CCDS) v.5.0, Ocaliva is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh (CP) Class B or C) or a prior decompensation event and in patients with complete biliary obstruction. Per the 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 accelerated or conditional 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 pharmacodynamic (PD) effects of OCA on high-density lipoprotein cholesterol (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 safety reasons.

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 European Association for the Study of the Liver (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. In patients with impaired renal function, especially those patients in whom creatinine clearance (CrCl) 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 CrCl 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 A). 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, ALP, aminotransferases, and albumin, and a normal prothrombin index) than subjects treated with placebo + UDCA (31% versus 0%) (Corpechot 2018).

Overall, 424 adverse events (AEs) were reported in 88 subjects (49% in the BZF group and 51% in the placebo group). 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 [AIH]) (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%).

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

5.4.3. Obeticholic Acid and Bezafibrate in Combination

Results from Phase 2 studies (Studies 747-213 and 747-214) demonstrated that OCA in combination with BZF provides substantial improvements in key biochemical markers. At Week 12, the greatest reductions in ALP were observed in the OCA + BZF 400 mg treatment groups, with an increase in treatment effect with the addition of OCA compared to BZF 400 mg alone. In Study 747-213, treatment with OCA 5-10 mg + BZF 400 mg SR resulted in least square (LS) mean absolute reduction in ALP of 196.4 U/L (62.3%) compared to a 134.2 U/L

(45.1%) reduction in the Placebo + BZF 400 mg SR active comparator arm. In Study 747-214, treatment with OCA 5 mg + BZF 400 mg immediate release (IR) resulted in a LS mean absolute reduction in ALP of 183.1 U/L (61.4%) compared to a 164.2 U/L (54.2%) reduction in the Placebo + BZF 400 mg IR active comparator arm.

Safety data from Phase 1 Study 747-123 and the first 6 months of Phase 2 Studies 747-213 and 747-214 indicated that OCA + BZF was generally well tolerated. The majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. No SAEs have been reported in Study 747-123. In the first 6 months Study 747-213, three SAEs were reported (hypertension, pruritus, and breast cancer). In the first 6 months of Study 747-214 three SAEs were reported (pneumonia, basal cell carcinoma, and intraductal proliferative breast lesion). No TEAEs leading to death have been reported across the 3 studies.

5.5. Rationale for Study Design and Dose for Investigational Product

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 prospective, double-blind randomized study, addition of 400 mg/day BZF in patients 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 an 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 mg/day to 10 mg/day) and fibrates (BZF 200 mg/day to 400 mg/day or fenofibrate 100 mg/day to 200 mg/day), along with UDCA (13 mg/kg/day to 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 to 24.8). The average UDCA dose was 15.4 (4.0) mg/kg/day (range 7.6 to 24.6) and 11 (19%) subjects had PBC-AIH overlap (Soret 2021).

Twenty-nine 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) years 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% to 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% to 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 to 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 to 16.7; p<0.001) for the Paris-2 criteria and 9.2 per year (95% CI: 3.4 to 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 to 58.7; p<0.001) for the Paris-2 criteria and 30.7 per year (95% CI: 4.7 to 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% to 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 to 6.9; p=0.08). Group OCA-Fibrate had an odds ratio of no pruritus at 9.9 per year (95% CI: 1.5 to 67.1; p<0.05) and was not significant in Group Fibrate-OCA. At the end of the study period, no subjects discontinued TT.

BZF therapy also has demonstrated benefits beyond improvements in liver function. In an AASLD Conference (AASLD 2019), data on patients receiving BZF (400 mg) or placebo for a period of 21-days was presented (de Vries 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).

Further, as described above, results from Study 747-213 demonstrated that at Week 12, the greatest reduction in ALP was observed in the OCA 5-10 mg + BZF 400 mg SR treatment group, with a clear increase in treatment effect with the addition of OCA compared to BZF 400 mg SR alone. Similarly, in Study 747-214, at Week 12 the greatest reduction in ALP was observed in the OCA 5 mg + BZF 400 mg IR treatment group, with an increase in treatment effect with the addition of OCA compared to BZF 400 mg IR alone.

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 Study 977-311 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 Dose and Bezafibrate Dose 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.

Preliminary Data from a Phase 1 study in healthy volunteers (Study 747-123 Part A) tested combinations of OCA and BZF to evaluate the safety and PK of the two drugs when co-administered. OCA was dosed at [redacted] mg, and BZF was dosed at [redacted] mg, resulting in 9 combinations. The preliminary data indicated that there was no meaningful effect of OCA on the concentrations of BZF in any combination.

Results from Study 747-214 demonstrated that OCA 5 mg in combination with BZF 400 mg was as effective as OCA 10 mg in combination with BZF 400 mg at Week 12 and beyond.

5.5.2.2. Bezafibrate Dose

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

SR 400 mg is the daily dose 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). Nine review studies (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).

In an analysis of the ITT population, in both Study 747-213 (BZF 400 mg SR ± OCA) and Study 747-214 (BZF 400 mg IR ± OCA), BZF 400 mg SR demonstrated ability to lower ALP and total bilirubin and improve tolerability (pruritus) at Month 3. In all instances, regardless of formulation and combination with OCA, BZF 400 mg led to greater reductions in ALP and total bilirubin relative to BZF 100 mg and 200 mg at Month 3. Across all treatment groups and irrespective of OCA or BZF dose or formulation, TEAEs were balanced across both Study 747-213 and Study 747-214. Collectively, the greatest improvement in ALP, total bilirubin, and tolerability was achieved with 400 mg BZF SR.

All subjects will be transitioned to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) once daily dose upon rolling over to this study.

5.6. Summary of Known Potential Benefits and Risks with Investigational Product

5.6.1. Benefits

The Sponsor plans to evaluate the combination of OCA + BZF for the treatment of PBC, including development of a 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).

4. Results from Phase 2 clinical studies (747-213 and 747-214) have demonstrated an increased treatment effect with the addition of OCA compared to BZF alone.

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 A). In a published Phase 3, randomized, double-blind, placebo-controlled study of treatment with BZF 400 mg/day for 24 months in 100 PBC subjects with an inadequate biochemical response to UDCA, BZF was reported to improve biochemical prognostic markers, liver stiffness progression, and pruritus (Corpechot 2018). This study also provided important information concerning the safety and tolerability profile of BZF when used long-term in subjects with PBC.

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

The AASLD guidance for the management of PBC states that fibrates can be considered as off-label alternatives for patients with PBC and inadequate response to UDCA (Lindor 2019). Additionally, the current 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 977-311 as a Phase 3, open-label, LTSE study to assess the safety and tolerability of the OCA + BZF FDC tablet in subjects with PBC.

5.6.2. 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.
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 v5.0, 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. Ocaliva is also contraindicated in patients with compensated cirrhosis with evidence of portal hypertension (e.g. ascites, gastroesophageal varices, persistent thrombocytopenia).
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 days, 158 days, 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 MASH, 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; MASH=Metabolic dysfunction-associated steatohepatitis; OCA=obeticholic acid; PBC=primary biliary cholangitis; PEY=patient exposure years
Sources: 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 ALP. 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 months 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.

BZF=bezafibrate; CK=creatine kinase; 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, BZF should be stopped, and appropriate symptomatic and supportive therapy should be administered as necessary. There is no specific antidote. Because BZF is highly bound to plasma proteins, hemodialysis should not be considered.

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

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

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.

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

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 BZF and OCA concomitantly and the Phase 2 study data to date, 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, Bezalip 2016, Bezalip 2020) and has also been reported in OCA clinical studies at higher doses in subjects with metabolic dysfunction-associated steatohepatitis (MASH). Section 7.5 provides detailed guidelines for the medical management of subjects with symptomatic cholelithiasis and/or cholecystitis.

Treatment with drugs of the fibrate class including BZF has been associated on rare occasions with myositis or rhabdomyolysis. Myopathy should be considered in any subject with diffuse myalgias, muscle tenderness/weakness, or marked elevations in CK levels, and dose adjustment may be needed in subjects with impaired renal function. Subjects should be advised to report unexplained muscle pain, tenderness or weakness promptly, particularly if accompanied by malaise or fever. Creatine kinase (CK) levels should be assessed in subjects reporting these symptoms, and investigational product should be interrupted if markedly elevated CK levels (≥5x ULN or ≥3x ULN with symptoms of rhabdomyolysis) occur or myopathy is diagnosed (Table 4). Section 7.4.4.3 provides detailed guidelines for evaluating and monitoring subjects with potential myopathy. In cases of rhabdomyolysis, administration of investigational product 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 AND PURPOSE

6.1. Primary Objectives

The primary objective is to assess the long-term safety and tolerability of the OCA + BZF FDC tablet in subjects with PBC.

6.2. Efficacy Objectives

The efficacy objective is to assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following:

- Biochemical disease markers, including ALP, GGT, ALT, AST, and total and conjugated bilirubin
- ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline
- Noninvasive assessments of liver fibrosis (transient elastography [TE], enhanced liver fibrosis [ELF] score)
- Disease severity scores (GLOBE, UK-PBC, and model of end-stage liver disease [MELD])

6.3. Exploratory Objectives

[redacted]

[redacted]

– MELD score ≥15

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

7.1.1. Methodology

This Phase 3, open-label, LTSE study will evaluate the safety, tolerability, and efficacy of the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) in approximately 133 subjects with PBC for up to 60 months (5 years).

- For subjects from Study 747-213 or Study 747-214 who continue to meet that protocol's requirements, they will transition into Study 977-311 once the study is active at their respective sites. The time subjects have spent in the LTSE phases in their respective studies, 747-213 or 747-214, will not count toward the 60 months in Study 977-311.
- Eligible subjects from other Sponsor studies may also transition to Study 977-311.

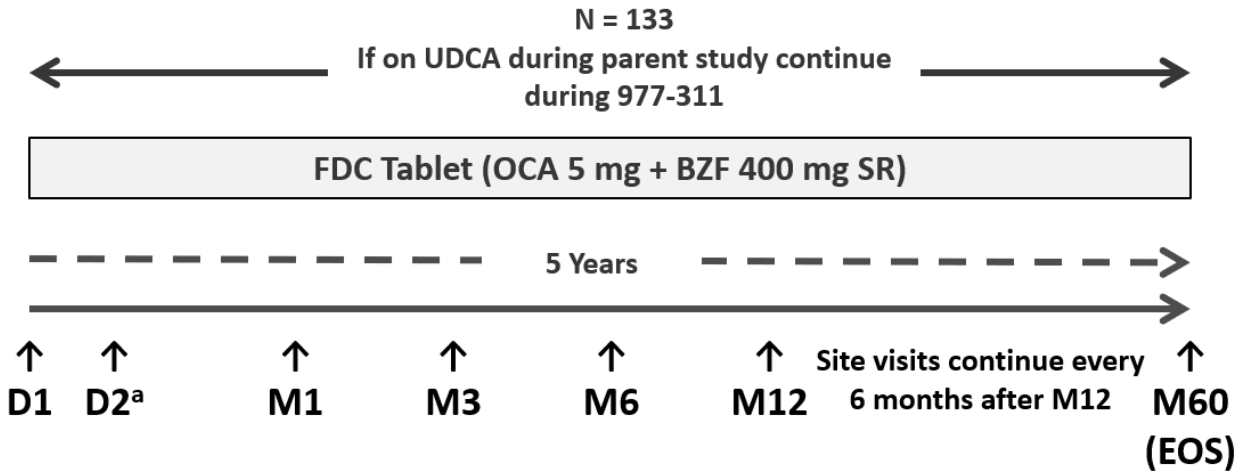
All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits) starting on Day 2. All subjects should continue their prestudy dose of UDCA throughout study participation.

After the Day 1, Day 2, Month 1, Month 3, Month 6, and Month 12 visits, subsequent in-clinic study visits will occur every 6 months for the assessment of safety, tolerability, efficacy, PK, and PD.

The study design diagram is presented in Figure 1.

7.1.2. Study Design Diagram

Figure 1: Study Design Schematic



BZF=bezafibrate; D=day; EOS=end of study; FDC=fixed-dose combination; IP=investigational product; LTSE=long-term safety extension; M=month; OCA=obeticholic acid; SR=sustained release; UDCA=ursodeoxycholic acid

Notes: Subjects taking UDCA at the time of enrollment will remain on their stable dose of UDCA during the study. Subjects will be re-consented.

Subjects in either Study 747-213 or Study 747-214 may already be in LTSE. The time subjects spent in LTSE on either study will not be carried over into this study, 977-311. Subjects will spend a total of 60 months (5 years) in Study 977-311.

[a] The Day 2 Visit can be either a virtual or onsite visit. It will be scheduled on Day 2 to Day 7 of the study depending on when laboratory results are available and reviewed. Subjects can elect to pickup IP onsite (onsite Day 2 visit) or have it shipped directly to them (virtual Day 2 visit). For subjects that have IP shipped, the Day 2 virtual visit should be scheduled once the subject receives IP.

7.1.3. Schedule of Study Procedures

Table 3: Schedule of Study Procedures

Study Visit	Day 1	Day 2 Visit (Day 2 to Day 7)[a]	M1	M3	M6	M12	Every 6 Months from M12	ET[b]	M60 (EOS)
Visit Window			±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±1 week	±2 weeks
Fast ≥8 Hours Prior to Visit[c]	X		X	X	X	X	X	X	X
Informed Consent Form	X								
Inclusion/Exclusion Criteria	X	X[d]							
Concomitant Medications	X	X	X	X	X	X	X	X	X
Myopathy Evaluation and Monitoring[e]	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X	X
Height	X								
Weight (including BMI and waist-hip ratio)[f]	X		X	X	X	X	X	X	X
Vital Signs[g]	X		X	X	X	X	X	X	X
12-Lead ECG	X							X	X
AEs[h]	X	X	X	X	X	X	X	X	X
CP Assessment[i]	X		X	X	X	X	X	X	X
MELD Score[j]	X		X	X	X	X	X	X	X
MRS	X		X	X	X	X	X	X	X
[redacted]									
GLOBE and UK-PBC[l]	X		X	X	X	X	X	X	X
[redacted]									
Administer IP[m]		X[n]	X	X	X	X	X		
Dispense IP		X[a]	X	X	X	X	X		
Assess IP Accountability and Compliance		X[o]	X	X	X	X	X	X	X
Serum Chemistry, Hematology,	X		X	X	X	X	X	X	X

Study Visit	Day 1	Day 2 Visit (Day 2 to Day 7)[a]	M1	M3	M6	M12	Every 6 Months from M12	ET[b]	M60 (EOS)
Visit Window			±2 weeks	±2 weeks	±2 weeks	±2 weeks	±2 weeks	±1 week	±2 weeks
Coagulation[p] (including CK)									
Virology (HCV/HBsAg)	X								
Urinalysis	X		X	X	X	X	X	X	X
Urine-Based β-hCG Pregnancy Test[q]	X		X	X	X	X	X	X	X
TE[r]	X		X	X	X	X	X	X	X
ELF score	X		X	X	X	X			
[redacted]									

AE=adverse event; [redacted]; β-hCG=Beta-human chorionic gonadotropin; BMI=body mass index; [redacted]; CP=Child-Pugh; CK=creatine kinase; ECG=electrocardiogram; EDC=electronic data capture; eCRF=electronic case report form; eGFR=estimated glomerular filtration rate; ELF=enhanced liver fibrosis; EOS=end of study; ET=early termination; [redacted]; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; IP=investigational product; M=month; MELD=model of end-stage liver disease; MRS=Mayo Risk Score; [redacted] PK=pharmacokinetic; [redacted]; QOL=quality of life; TE=transient elastography; UDCA=ursodeoxycholic acid

Notes: Unscheduled visits should occur as needed in the event of signs or symptoms of suspected hepatic injury or decompensation or if laboratory alerts have been triggered. Subjects who discontinue investigational product but continue in the study may be requested to come in for an Unscheduled Visit at the discretion of the Investigator depending on the timing of their next scheduled study visit. Unscheduled visits are optional and should occur as needed based on Investigator discretion; a PK sample should be collected if an unscheduled visit occurs due to a safety event.

[a] The Day 2 Visit can be either a virtual or onsite visit. It will be scheduled on Day 2 to Day 7 of the study depending on when laboratory results are available and reviewed. Subjects can elect to pickup IP onsite (onsite Day 2 visit) or have it shipped directly to them (virtual Day 2 visit). For subjects that have IP shipped, the Day 2 virtual visit should be scheduled once the subject receives IP.

[b] An ET visit should occur in subjects who withdraw from the study. The ET visit should be completed as near as possible to the subject's last dose of IP. Study procedures and assessments are not required if previously completed within 4 weeks of the ET.

[c] Subjects should be instructed to fast overnight (at least 8 hours) before all in-clinic study visits, but water is permitted. Record fasting status in the source and eCRF. If the subject reports having eaten or drunk anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all onsite study visits.

[d] On the Day 2 Visit, the Investigator will review Day 1 eligibility laboratory results. If any laboratory results are out of range, the Medical Monitor and Sponsor Medical Monitor will review and determine an appropriate plan for the subject on a case-by-case basis.

[e] If subjects develop 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 every 2 weeks until values return to baseline levels.

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

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

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

[i] CP Score will be calculated based on central laboratory evaluations and a targeted assessment of ascites and hepatic encephalopathy. Scores will be recorded on the eCRF.

[j] MELD score will be calculated from serum chemistry and other parameters collected at the same visit. Scores will be recorded on the eCRF.

[redacted]

[l] GLOBE and UK-PBC scores will be calculated from serum chemistry and other parameters and recorded on the eCRF.

[m] At each study visit, the dose of investigational product should be administered daily at the same time (AM dosing is preferred to align with all study visits) starting on Day 2. All assessments must be completed before administration of investigational product and UDCA (if applicable).

[n] Subjects who have an onsite Day 2 visit will be administered investigational product onsite. Subjects who have a virtual Day 2 visit will self-administer investigational product during the virtual visit.

[o] For subjects who have a virtual day 2 visits and have had IP shipped, the Investigator to confirm that IP was received in good condition, was untampered, and is the correct drug. Date of first IP administration should be recorded.

[p] See analytes listed in Table 11.

[q] Urine-based β-hCG pregnancy tests must be performed in females of childbearing potential (defined in Section 9.7.2.1) prior to entry and at every visit. If positive, a confirmatory serum pregnancy (quantitative β-hCG) blood test must be performed at the central laboratory. If the confirmatory blood test is also positive, the subject may not continue in the study taking IP. (Additional testing may be conducted where required, regionally.)

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

[redacted]

7.1.4. Study Duration

The total duration of Study 977-311 per subject will be a maximum of 60 months from day of study entry. The end of study is defined as the date of the last visit of the last subject.

7.2. Number of Subjects

Up to approximately 133 subjects transitioned from Study 747-213 or Study 747-214 (or other Sponsor studies) who continue to meet this protocol's requirements.

7.3. Planned Dosing Regimen

Subjects who continue to meet this protocol's requirements will receive the FDC tablet (OCA 5 mg + BZF 400 mg SR), once daily.

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. CP and MELD scores will be reviewed at each visit where labs are drawn (Section 7.4.4 and Section 14.2.1). CP Scores should only be applied in subjects who have evidence of cirrhosis or progression to cirrhosis based on criteria presented in Section 7.4.4. In addition, AEs, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in Section 7.1.3. Based on the assessments of signs and symptoms of hepatic injury and/or muscular injury and liver biochemistry (Section 7.4.1 and Section 7.4.2), the investigational product (OCA + 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 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 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 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 8.4.1), (4) documentation in the AE electronic case report form (eCRF) or the SAE eCRFs (Section 14.1.4.1 and Section 14.1.4.2), and (5) contact with the Medical Monitor (Section 14.1.6).

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

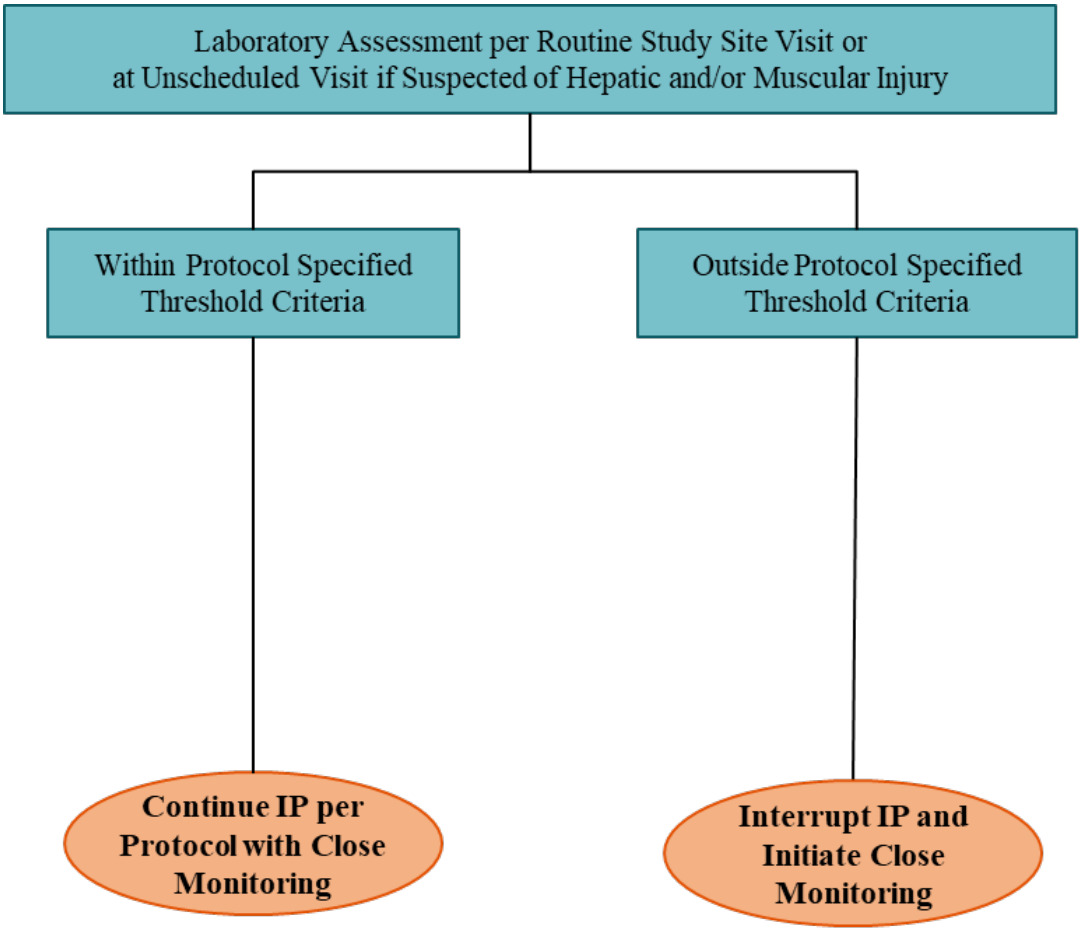
Liver biochemistry and serum CK will be assessed to evaluate for potential hepatic and/or muscular injury or hepatic decompensation. These assessments will be performed at:

- Each protocol-specified visit (Table 3)
- 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



CK=creatine kinase; INR=international normalized ratio; IP=Investigational Product; PK=pharmacokinetic
Notes: Laboratory assessments include: ALT, ALP, AST, GGT, direct and total bilirubin, INR, and CK.
PK sampling should be conducted within 7 days of IP interruption; close monitoring including physical exams and repeat biochemistry labs should occur as often as deemed appropriate by the Investigator (Table 4).

Table 4: 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

BL=baseline; CK=creatine kinase; DILI=drug-induced liver injury; INR=international normalized ratio; IP=investigational product; N/A=not applicable; TB=total bilirubin

[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 Month 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 every 2 weeks until values return to baseline levels; same criteria apply to considering re-initiation of IP. CK levels should be assessed in patients reporting symptoms of rhabdomyolysis, and investigational product 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 5.

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.

Table 5: Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Mandatory Discontinuation of Investigational Product

- Clinical evidence of portal hypertension, defined as
  - Platelet count <150,000/µL
  - Splenomegaly on ultrasound
  - Non-bleeding varices on endoscopy
- Evidence of hepatic decompensation
  - Progression to CP score ≥7
  - Ascites including hepatic hydrothorax
  - Hepatic encephalopathy – requiring hospitalization and/or lactulose and/or rifaximin
  - Hepatorenal syndrome (Type 1 or Type 2), hepatopulmonary syndrome, or portopulmonary syndrome
  - Variceal hemorrhage
  - Jaundice (with total bilirubin >3 mg/dL [>51.3 µmol/L])
  - MELD ≥15
- HCC
- Any liver-related event requiring hospitalization and treatment
- Evaluation, listing, or completion of a liver transplant

CP=Child-Pugh; HCC=hepatocellular carcinoma; MELD=Model for End-stage Liver Disease

7.4.4. Child-Pugh Score

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 6 and can range from 5 to 15. The Investigator should ensure all lab data is entered into the eCRF. Although CP score calculation will automatically be computed in all subjects (at all times data is obtained for the eCRF), it should only be applied to subjects who meet the criteria for progression to cirrhosis (see Section 7.4.4.1). 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 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 6: Child-Pugh Scoring System

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

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
  - 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 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 Day 1/Day 2: Check baseline CK: If ≥5x ULN the Medical Monitor and Sponsor Medical Monitor will determine if the subject can continue in Study 977-311 on a case-by-case basis.
- 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 4).

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, particularly with any suspicion of biliary obstruction, investigational product should be promptly interrupted. Treatment with investigational product may be resumed if an alternative probable cause has been found and resolution has occurred.

Investigational product should be discontinued in the following instances:

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

7.6. Dosage Adjustment Criteria

Dose frequency may be modified for the management of pruritus as described in Section 14.1.3.1. 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 should be requested to continue with study visits until Month 60/end of study (EOS). Subjects who discontinue investigational product may be requested to come in for an Unscheduled Visit at the discretion of the Investigator depending on the timing of their next scheduled study visit.

Refer to Section 8.4.1 for guidance on mandatory discontinuation of investigational product due to severe and related AEs. Refer to Section 8.4.2 for other reasons of discontinuation of investigational product (e.g., withdrawal of consent, lost to follow-up, or pregnancy).

Subjects who were taking UDCA should continue this as a concomitant medication for the entirety of the study 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 60 investigational study sites, globally, with experience in treating subjects with PBC. Subjects will be transitioning from Study 747-213 and Study 747-124 (or other Sponsor studies) if they continue to meet the following criteria.

8.2. Subject Inclusion Criteria

1. All subjects with PBC who participated and are actively taking investigational product in Study 747-213 or Study 747-214 (or other Sponsor studies) are eligible to enroll in this study (977-311).

- Subjects on a drug holiday within the previous 60 days due to unresolved TEAEs or SAEs in the parent study should discuss eligibility for rolling over to this study with the Sponsor Medical Monitor.

2. 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 at least 30 days after the last dose of investigational product. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from exposure to investigational medicinal products. Highly effective methods of contraception are as follows:
   - Intrauterine device
     - Intrauterine device
     - Intrauterine hormone-releasing system
   - 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 of their parent study.
   - 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 of their parent study.
   - 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 30 days 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.
3. Male subjects who are sexually active with female partners of childbearing potential (defined in Section 9.7.2.1) must agree to use a condom with spermicide and to use (or have their partner use) 1 other approved method of highly effective contraception from the initiation of the study and until at least 90 days after the last dose of investigational product as listed in Inclusion Criterion #2.
4. Male patients must refrain from sperm donation from the initiation of the study and until at least 90 days after the last dose of investigational product.

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

8.3. Subject Exclusion Criteria

1. Any history or presence in the last 30 days, before rolling over to this study, of other concomitant liver diseases, including any of the following:
   - Hepatitis C virus (HCV) infection with positive RNA
   - 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 and Sponsor Medical Monitor
     - Subjects should be excluded if positive HBV DNA or HCV RNA
   - PSC
   - Alcoholic liver disease
   - Definite autoimmune liver disease or PBC-AIH overlap
   - MASH
   - Gilbert's Syndrome (due to interpretability of bilirubin levels)
   - Rare liver conditions such as Wilson's disease, hemochromatosis, alpha-one anti-trypsin deficiency, or other conditions identified by the Principal Investigator
2. Clinical complications of PBC including:
   - Prior liver transplantation
3. Any history or presence in the last 30 days, before rolling over to this study, of any one of the following decompensating events:
   - CP Score ≥7
   - Clinical evidence of decompensated liver disease or evidence of portal hypertension, including but not limited to:
     - Varices (including a history of esophageal varix ligation or asymptomatic esophageal varices by endoscopy)
     - 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 >ULN

  - 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 II) or serum creatinine >1.5 mg/dL (135 µmol/L) or estimated glomerular filtration rate (eGFR) <60 mL/min from the last lab assessment/visit in parent study, before transitioning to Study 977-311
- Portopulmonary hypertension
- Hepatopulmonary syndrome

4. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) or that 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. Evidence or history of cholelithiasis or choledocholithiasis unless documented cholecystectomy. Gallbladder polyps if >5 mm in diameter
7. History of chronic pancreatitis or recurrent acute pancreatitis – defined as at least 2 episodes of acute pancreatitis, with symptoms resolving between each episode
8. History of drug-induced myopathy
9. Chronic kidney disease (serum creatinine >1.5 mg/dL [>135 µmol/L]; CrCl <60 mL/min) or undergoing dialysis
10. Platelet count <150,000/µL at the last visit in parent study, before transitioning to Study 977-311
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, QT interval of the electrocardiogram (QT) or QT interval of the electrocardiogram corrected (QTc) interval of >450 milliseconds for males and >470 milliseconds for females
13. Severe pruritus, or required systemic treatment for pruritus (e.g., with bile acid sequestrants [BAS] or rifampicin) within 2 months of Day 1 of Study 977-311. Subjects who plan to use or will use BAS during the study will not be eligible.
14. History of known or suspected clinically significant (CS) hypersensitivity to OCA, BZF, or other fibrates or any of their components

15. Known photoallergic or phototoxic reactions to fibrates
16. If female, known pregnancy, a positive urine pregnancy test (confirmed by a positive quantitative serum pregnancy test), or current lactation at the last visit in parent study, before transitioning to Study 977-311
17. Other CS medical conditions that are not well controlled or for which medication needs are anticipated to change during the study (e.g., Type 2 diabetes mellitus, hypothyroidism, nephritic or nephrotic syndrome, dysproteinemia, obstructive biliary disease, dyslipidemia), and/or up to the discretion of the Principal Investigator
18. Treatment with the following medications 30 days before Day 1 of Study 977-311, or plans to use these medications during the study: azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline, rifampicin, statins, budesonide and other systemic corticosteroids (short-term use up to 2 weeks is permitted), monoamine oxidase inhibitors (MAOIs), and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazid, and nitrofurantoin)
19. Treatment with the following medications within 12 months before Day 1 of Study 977-311, or plans to use these medications during the study: antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
20. Participation in a study of another investigational medicine or device within 30 days before Day 1 of Study 977-311 (except for Study 747-213, Study 747-214, or other eligible Sponsor study)
21. History of or ongoing alcohol or drug abuse within 1 year before Day 1 of Study 977-311. Subjects with moderate alcohol use within 3 months prior to the last visit in parent study, before transitioning to Study 977-311, 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), or 1.5 ounces of 80 proof (40% alcohol)
22. History of noncompliance with medical regimens, or is considered by the Principal Investigator not able to meet the requirements as specified in the protocol from Day 1 throughout the duration of the study
23. Blood or plasma donation within 30 days before Day 1
24. Mental illness or other condition which may impair decision making, such that the validity of informed consent or ability to be compliant with the study is uncertain
25. A CK value on Day 1 of Study 977-311 ≥5x ULN or any abnormal laboratory value that is considered CS in the opinion of the Principal Investigator and Sponsor at the last visit in parent study, before transitioning to Study 977-311
26. Known or suspected nephrotic syndrome in the last 30 days, before rolling over to this study, based on the following diagnostic criteria (both Type 1 and Type 2):
    - Proteinuria, spot urine protein: albumin/creatinine ratio (ACR) of >300 mg/mmol (subjects with normal renal function and ACR values analyzed to be below the lower limits of detection are permitted)

- Serum albumin <25 g/L
- Clinical evidence of peripheral edema
- Severe hyperlipidemia (total cholesterol above >10 mmol/L)

8.4. Subject Withdrawal Criteria

Subjects who are discontinued from investigational product should be requested to continue with study visits until Month 60/EOS. Subjects who discontinue investigational product may be requested to come in for an Unscheduled Visit at the discretion of the Investigator depending on the timing of their next scheduled study visit.

8.4.1. 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 5.

Investigational product will be discontinued permanently if the subject has evaluation, listing or completion, of a liver transplant or experiences other potential hepatic decompensation events as defined in Table 5. Subjects should be closely monitored until normalization or stabilization and should continue to return for scheduled study visits for safety follow-up.

8.4.1.1. Severe and Related Adverse Events

If a subject experiences an AE that is ≥Grade 3 in severity using criteria outlined in Section 14.1.3 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.

8.4.1.2. 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 14.1.10, pregnancy is not considered an AE for reporting purposes.

Subjects who plan to become pregnant after study discontinuation or withdrawal should consult with their study doctor or primary HCP.

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

Subjects who discontinue investigational product will be requested to continue in the study until the end of the study or at the discretion of the Sponsor; however, subjects are free to discontinue at any time.

The following events are considered appropriate reasons for a subject to be withdrawn from the study or discontinue investigational product. Subjects who discontinue investigational product 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 or Sponsor to be clinically important
- The development of any medical conditions listed in the exclusion criteria that might jeopardize patient safety (Section 8.3)

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 email as soon as possible if any subject prematurely withdraws from the study.

The Sponsor may terminate this study at any time.

8.4.2.1. 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.

8.4.2.2. Lost to Follow-Up

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

8.4.3. 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.

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

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

9.1.1. Treatment Assignment

The term "investigational product" (provided as part of this clinical study) refers to the following:

- FDC tablet (OCA 5 mg + BZF 400 mg SR), once daily

Investigational product will be taken orally with water, once daily for the duration of the study. The FDC tablet must be swallowed whole and not be chewed, divided, or crushed and must be taken with food and water (ad libitum) throughout the study period. Subjects are requested to take medication in the morning. Specific instructions for dosing will be provided for PK assessment days.

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 sample, concomitant medications should be taken after the 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.

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. Antimicrobial

Rifampin should be used with caution in patients with PBC due to the hepatotoxicity concerns as specified in the rifampin USPI.

9.2.8. Drug-Drug Interaction

OCA

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. OCA 10 mg and 25 mg increased exposure to the sensitive cytochrome P (CYP) 1A2 probe, caffeine, by 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, or elicit a PK drug-drug interaction, slight decreases in INR were observed suggesting a potential to alter warfarin efficacy.

BZF

For BZF, caution should be exercised when coumarin-type 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.

3-hydroxy-3-methylglutaryl coenzyme A (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 not be administered together with HMG CoA reductase inhibitors. Subjects receiving this combination therapy must be fully educated or fully informed carefully of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the

first signs of myopathy. This combination therapy must not be used in subjects with predisposing factors for myopathy (impaired renal function, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance, and a high alcohol intake).

Cyclosporine: Severe myositis and rhabdomyolysis have occurred when a cyclosporine was administered with a fibrate. Therefore, the benefits and risks of using BZF SR concomitantly with cyclosporine should be carefully considered and is up to the 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 subjects and in the event of relevant significant changes in laboratory parameters, BZF should be discontinued.

Insulin and sulphonylurea: serious hypoglycaemia may result from 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 4 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 subjects taking estrogens or estrogen-containing contraceptives must be critically considered on an individual basis.

Rosiglitazone: Some epidemiologic studies and case reports suggest that markedly decreased high density lipoprotein cholesterol in some 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 after Day 2.

Subjects should be instructed to retain all bottles of investigational product, even if empty, and to provide 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 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

There are no treatment groups, as this is a single-arm study.

9.4.2. Blinding

Blinding is not applicable to this open-label, single-arm study.

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). The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-, which is 311- for this study). The next 6 digits (BBBCCC) represent the unique subject identification (ID).

9.6. Restrictions

All subjects must fast for at least 8 hours before all study visits. All analytes will be assayed in fasting serum or plasma samples (Table 3). Water is permitted during the fasting period.

9.7. Visit Procedures

The visit procedures are provided in Table 3. 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. LTSE Period

Subjects from Study 747-213 or Study 747-214 (or other Sponsor studies) will transition into Study 977-311 once the study is active at their respective sites. The time subjects have spent in the LTSE phases in their respective parent studies will not count toward the 60 months in Study 977-311.

All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits) starting on Day 2. All subjects should continue their prestudy dose of UDCA throughout study participation.

9.7.2.1. Day 1

The following procedures will be performed as listed in Table 3:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all onsite study visits
- Review ICFs and obtain signatures before performing any study-related procedures
- Verify inclusion and exclusion criteria for eligibility
- Record concomitant medications
- Assess and record any pretreatment AEs including myopathy evaluation (after the ICF has been signed)
- Perform physical examination
- Measure height and record weight and body mass index (BMI) and waist-to-hip ratio (WHR)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Perform standard 12-lead electrocardiogram (ECG)
- Calculations will be performed for the following:
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - MELD Score: to be calculated from serum chemistry and other parameters
  - MRS

[redacted]

  - GLOBE and UK-PBC scores

[redacted]

- Obtain blood samples for the following:
  - Serum chemistry, hematology, and coagulation; see analytes listed in Table 11.
  - Virology: HCV/HBsAg
  - A dedicated serum sample will be collected and sent to the vendor for laboratory testing and calculation of ELF score

- 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.
- TE (only if test is available at qualified sites)
- Remind subject to fast at least 8 hours prior to next onsite visit

9.7.2.2. Day 2

The Day 2 Visit can be either a virtual or onsite visit. The following procedures will be performed as listed in Table 3:

- Verify inclusion and exclusion criteria for eligibility. The Investigator will review Day 1 eligibility laboratory results. If any laboratory results are out of range, the Medical Monitor and Sponsor Medical Monitor will review and determine an appropriate plan for the subject on a case-by-case basis.
- Record concomitant medications
- Assess and record any pretreatment AEs including myopathy evaluation
- Dispense investigational product for subjects still eligible for study. Subjects can elect to pickup investigational product onsite (onsite Day 2 visit) or have it shipped directly to them (virtual Day 2 visit). For subjects that have investigational product shipped, the Day 2 virtual visit should be scheduled once the subject receives investigational product.
- Administer investigational product for subjects still eligible for study. Subjects who have an onsite Day 2 visit will be administered investigational product onsite. Subjects who have a virtual Day 2 Visit will self-administer investigational product during the virtual visit.
- Assess investigational product accountability and compliance. For subjects who have a virtual Day 2 Visit and have had investigational product shipped, Investigator to confirm that investigational product was received in good condition, was untampered, and is the correct drug. Date of first investigational product administration should be recorded.
- Remind subject to fast at least 8 hours prior to next onsite visit

9.7.2.3. Month 1, Month 3, Month 6, and Month 12

The following procedures will be performed as listed in Table 3:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all onsite study visits
- Record concomitant medications
- Assess and record any AEs including myopathy evaluation
- Perform 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 for the following:
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - MELD Score: to be calculated from serum chemistry and other parameters
  - MRS
  - [redacted]
  - GLOBE and UK-PBC scores

[redacted]

- Obtain blood samples for the following:
  - Serum chemistry, hematology, and coagulation; see analytes listed in Table 11
  - A dedicated serum sample will be collected and sent to the vendor for laboratory testing and calculation of ELF score

[redacted]

- Urinalysis
- Perform a urine-based 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.

- TE (only if test is available at qualified sites)
- Dispense/administer investigational product
- Assess investigational product accountability and compliance
- Remind subject to fast at least 8 hours prior to next visit

9.7.2.4. Every 6 Months from Month 12, ET, and Month 60 (EOS)

The following procedures will be performed as listed in Table 3:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having drunk or eaten anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all onsite study visits
- Record concomitant medications
- Assess and record any AEs including myopathy evaluation
- Perform 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)
- Perform standard 12-lead ECG only at ET and Month 60 (EOS)
- Calculations for the following:
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.
  - MELD Score: to be calculated from serum chemistry and other parameters
  - MRS
  - [redacted]
  - GLOBE and UK-PBC scores

[redacted]

- Obtain blood samples for the following:
  - Serum chemistry, hematology, and coagulation; see analytes listed in Table 11

[redacted]

- Urinalysis
- Perform a urine-based 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.
- TE (only if test is available at qualified sites)
- Dispense/administer investigational product (not at ET or Month 60)
- Assess investigational product accountability and compliance
- Remind subject to fast at least 8 hours prior to next visit (not at Month 60)

9.7.3. Unscheduled/Safety Visit

The Investigator may schedule an Unscheduled/Safety Visit at any time if clinically warranted based on Investigator discretion. Subjects who discontinue investigational product but continue in the study may be requested to come in for an Unscheduled Visit at the discretion of the Investigator depending on the timing of their next scheduled study visit. These subjects will then be requested to continue with regularly scheduled study visits until Month 60/EOS.

A PK sample should be collected if an unscheduled visit occurs due to a safety event. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted at the discretion of the Investigator. As appropriate, the Medical Monitor should be contacted.

9.8. COVID-19 Vaccine

COVID-19 vaccination is allowable for subjects enrolled in this trial. Of note, as the currently approved COVID-19 vaccines have not been specifically tested in the PBC patient population, there are no safety data available specific to use of COVID-19 vaccines in patients with PBC.

If a participant has received a COVID-19 vaccination at any time, the date(s) of vaccination(s), vaccine name, batch number, and manufacturer should be recorded as a concomitant medication for each dose.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

The FDC investigational product will be supplied as white, oval, film-coated tablets. The FDC tablet combines OCA and BZF in a single tablet. The FDC tablet formulation is a bilayer, film coated tablet containing 2 active components: OCA 5 mg IR with BZF 400 mg SR. The FDC tablets are 9 mm by 19 mm oval tablets debossed with “INT” on 1 side and “3547” on the other side. Each FDC tablet contains [redacted] as a

release controlling agent for the active BZF along with the following inactive ingredients: [redacted] The FDC will be provided as tablets for oral administration in high density-polyethylene (HDPE) bottles with heat induction seals and child-resistant closures, containing 100 tablets. All FDC tablets will be manufactured according to Good Manufacturing Practice (GMP).

10.2. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to GMP standards by a designated qualified vendor. The investigational product will be provided as tablets for oral administration and provided in HDPE bottles with heat induction seals and child resistant closures. The bottle packaging will provide information about the treatment dose contained in the bottle. Multiple bottles may be dispensed to the subject according to the visit schedule in Table 3 to provide enough tablets for daily dosing until the next time investigational product is dispensed.

The designated investigational product packaging/distribution vendor will also be responsible for the distribution of the investigational product to the clinical sites.

10.3. Investigational Product Storage

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

10.4. Investigational Product Administration

Refer to Section 9.1.

10.5. 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.

11. EFFICACY ASSESSMENTS

11.1. Efficacy Laboratory Assessments

Refer to Table 11 for a full list of analytes to be tested. Laboratory assessments will be performed according to the schedule presented in Table 3.

11.2. Disease-Specific Symptoms as Assessed by Questionnaires

Data will be collected to determine the effects of OCA on health-related quality of life. Health-related quality of life assessments will take place during the visits indicated in Table 3.

The following health-related quality of life measures will be used to compare the effects of OCA alone or in combination with BZF:

[redacted]

11.3. GLOBE and UK PBC Scores

The GLOBE and UK-PBC scores will be calculated from serum chemistry and other parameters.

12. NONINVASIVE MEASUREMENTS OF LIVER STIFFNESS

The Fibroscan TE device (Echosens, Paris, France) will be used at all study sites that have the equipment to collect hepatic stiffness measurements. These study sites must have the staff trained in the use and data interpretation of the device. This is a validated and noninvasive technique used to assess hepatic stiffness, which will be conducted according to the schedule presented in Table 3.

[redacted]

ELF combines 3 serum markers (HA, P3NP, and TIMP-1) to quantify liver fibrosis. 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 ELF will be performed according to the schedule listed in Table 3.

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

13. CLINICAL PHARMACOLOGY ASSESSMENTS

Subjects who receive at least 1 dose of the OCA + BZF FDC tablet and have bioanalytical concentration data available that is not impacted by a study protocol deviation that impacts the PK 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.

13.1. PK Blood Sampling

All PK blood collections must be performed at the clinical site and not at a local lab.

Subjects need to be in fasting condition for at least 8 hours prior to collection of PK samples. A [redacted] through Month 60 (EOS), and the ET and/or Unscheduled Visits (if applicable). A [redacted] also must be collected within 7 days of a safety event (e.g., event related to potential hepatic or muscular injury).

The acceptable windows for sample collection on Month 1 through Month 60 Visits are shown in Table 7. There is no window required for the Day 1 Visit as investigational product will not be administered.

Table 7: Acceptable Windows for Pharmacokinetic Sample Collection (Month 1 through Month 60)

Nominal Sampling Time	Acceptable Sampling Window
[redacted]	30 minutes ±15 minutes before dosing

13.2. Bioanalysis

Plasma concentrations of OCA and its metabolites (glyco-OCA and tauro-OCA conjugates) will be determined using a validated liquid-chromatography mass spectrometry/mass spectrometry method.

BZF concentrations will be determined using appropriate validated bioanalytical methods. Metabolites of BZF (e.g., BZF-hydroxide, BZF-glucuronide, and others) may also be quantitated in this study if deemed appropriate.

PK samples collected in this study may be used for exploratory metabolic and bioanalytical purposes.

A description of each bioanalytical method validation used to quantify PK samples will be included with the plasma concentration data in separate bioanalytical reports.

13.3. Pharmacodynamic Assessments

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

14. SAFETY ASSESSMENTS

14.1. Adverse Events and Serious Adverse Events

14.1.1. Definitions of Adverse Events

14.1.1.1. 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 14.1.10.

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.

14.1.1.2. 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 an SAE.

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

14.1.1.3. Treatment-Emergent Adverse Events

A TEAE is any event not present before the initiation of the investigational product in this study or any event already present, which worsens in either severity or frequency following exposure to the investigational product in this study.

14.1.1.4. 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 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 7 days after knowledge by the Sponsor of such a case. Relevant follow-up information is subsequently communicated within an additional 8 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.

14.1.2. 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 8. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as suspected adverse reaction (SAR). "Reasonable possibility" means 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 8: 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

14.1.3. 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 9, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 9: Severity of Adverse Events

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

14.1.3.1. 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 10. In order to assess the potential improvement in pruritus with treatment, baseline pruritus presence (yes/no) and severity (as shown in Table 10) will be determined.

Table 10: 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. If the drug holiday lasts more than 30 days, the subject should be permanently discontinued from investigational product but requested to continue with study visits until Month 60/EOS.
- Per Section 8.4.1.1, 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.
- 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.
- Rifampin should be used with caution in patients with PBC due to the hepatotoxicity concerns as specified in the rifampin USPI.
- 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.

14.1.4. Reporting of Adverse Events and Serious Adverse Events

14.1.4.1. 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.

14.1.4.2. 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:

- Sending an SAE report form via email to: 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 the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators (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 IRBs/IECs 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 Investigator's Brochure (IB).

14.1.5. Overdose

An overdose is defined as administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information. When applying this definition, clinical judgement should always be applied (EMA 2017). The event of overdose should be carefully assessed and reported (e.g., intent, exposure, signs, symptoms, and potential confounders). PK sample must be collected. Patient-reported history of overdose must be assessed and documented regarding intent, exposure, and potential co-ingestants.

Per the CCDS v5.0, in clinical trials, patients with PBC who received OCA 25 mg QD (2.5-times the highest recommended dosage) or 50 mg QD (5-times the highest recommended dosage) experienced a dose-dependent increase in the incidence of hepatic adverse reactions, including elevations in liver biochemical tests (transaminase and bilirubin up to greater than 3x ULN), ascites, jaundice, portal hypertension, and PBC flares.

While there has been no reported case of overdosage in treatment with BZF, symptomatic and supportive measures should be taken. Because BZF is highly bound to plasma proteins, hemodialysis should not be considered. In patients with existing impaired renal function, if dosage recommendations are not followed, overdosage may occur and severe rhabdomyolysis may develop. Administration of BZF must be stopped immediately and renal function must be carefully monitored.

In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

14.1.6. Additional Investigator Responsibilities for SAEs

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

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

14.1.7. 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 14.1.4.2.

14.1.8. 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 14.1.4.2.

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 14.1.4.

14.1.9. 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 DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped.

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, Greenberg 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.

14.1.10. 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 8.4.1.2) and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy eCRF in the EDC system and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to sae@interceptpharma.com or faxed to +1 800 497 8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and Sponsor.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 14.1.4 must also be followed.

14.2. Other Safety Parameters

14.2.1. MELD Score

The MELD scoring system is used to assess the severity of chronic liver disease. The MELD score is useful in assessing patients with significant decompensation and the MELD score is now used by the United Network for Organ Sharing in the US and Eurotransplants to manage the organ allocation for liver transplantation. The threshold for placement on an organ transplantation queue varies between regions across the globe, but a score of 15 may result in a place on the transplant waiting list in the US.

An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. The MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival and is calculated according to the following formula (Kamath 2007):

MELD = 3.78 x ln(serum bilirubin [mg/dL]) + 11.2 x ln(INR) + 9.57 x ln(serum creatinine [mg/dL]) + 6.43

INR will be calculated based on PT value by the central laboratory.

MELD score will be reported in whole numbers on the eCRF according to the frequency listed in Table 3.

For a MELD score ≥15 to be considered as an outcome endpoint, an indication of the presence of cirrhosis and the progression of liver disease must be present. However, transient increases of total bilirubin, creatinine, or INR values due to causes other than progression of liver disease should be ruled out (e.g. use of medications that may cause an increase in INR). In addition, it should be ascertained by the adjudicators that the change in MELD score is sustained and not transient. Additionally, the subject must have MELD ≤12 at baseline (defined as the last assessment performed before the first dose of investigational product in Study 977-311).

14.2.2. 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

14.2.3. 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). 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 6).

14.2.4. 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.

14.2.5. Electrocardiogram

Standard 12-lead ECGs will be collected at the timepoints indicated in Table 3. ECGs will be recorded using the site's standard ECG equipment. Collection of additional ECGs for routine safety monitoring at additional timepoints 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.

14.2.6. Laboratory Assessments

Subjects should be instructed to fast overnight (at least 8 hours) before all study visits, but water is permitted. Record fasting status in the source and eCRF. If the subject reports having eaten or drunk anything other than water within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all onsite study visits.

Blood and urine samples for laboratory assessments will be collected at the visits indicated in Table 3.

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 CS 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 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 quantitative serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified, and the subject will be followed as outlined in Section 14.1.10 until pregnancy outcome.

CP, GLOBE, and UK-PBC scores will be calculated based on demographic, examination, and clinical laboratory values as described in the Statistical Analysis Plan (SAP).

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

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

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

The list of laboratory analytes to be tested is shown in Table 11.

Table 11: List of Laboratory Scores and Analytes

Laboratory Assessment	Scores and Analytes[a]
Serum chemistry	Albumin, ALP, BUN, creatinine, conjugated (direct) bilirubin, 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, free fatty acids, eGFR, CK, and CrCL
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
Noninvasive measurement of liver stiffness	[redacted] ELF, and markers of [redacted] TE
Virology	HCV, HBsAg
Pregnancy test (female subjects of childbearing potential)[b]	β-hCG
Disease Severity Scores	MELD, CP, GLOBE and UK-PBC scores
PD assessment	[redacted]
PK assessment	BZF, OCA and their metabolites

[redacted]; aPTT=partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; BZF=bezafibrate; [redacted] CrCL= creatinine clearance; CK=creatine kinase; CP=Child-Pugh score; eGFR=estimated glomerular filtration rate; ELF=enhanced liver fibrosis; 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; MELD=model of end-stage liver disease; OCA=obeticholic acid; PD=pharmacodynamic; PK=pharmacokinetic; [redacted] PT=prothrombin time; TE=transient elastography; TG=triglycerides; UK=United Kingdom; 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 quantitative serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified, and the subject will be followed through pregnancy outcome, as outlined in Section 14.1.10.

14.2.7. Health-Related Quality of Life

See for Section 11.2 for questionnaires to be used.

14.3. Hepatic and Renal Event Adjudication

All events of potential hepatic injury, suspected liver-related clinical outcomes, and potential renal injury that occur after administration of the first dose of the investigational product will be reviewed and adjudicated by independent and blinded adjudication committees, depending on event type.

Each adjudication committee has a charter that documents the reporting of events by the study site, definition of the potential events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

Specific details of the events that will be adjudicated are described in the respective adjudication charters. 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.

15. STATISTICS

An SAP providing details regarding the specific planned analyses will be prepared, finalized, and approved before any study snapshot. The SAP will be prepared as soon as planning for the statistical methods section of the protocol is initiated.

15.1. Analysis Populations

LTSE Population: The LTSE Population will include all subjects who receive at least 1 dose of the FDC tablet in Study 977-311.

Pharmacokinetic Population: The PK Population will include all subjects in LTSE population who receive the FDC tablet in Study 977-311 and have a PK sample(s) without any major protocol deviations that could potentially affect plasma exposure.

Pharmacodynamic Population: The PD Population will include all subjects with a baseline assessment and at least 1 on-treatment assessment without any major protocol deviations that could potentially affect results.

15.2. Determination of Sample Size

This is an estimation study with no formal hypothesis to be tested. Therefore, sample size is strictly based on number of subjects being captured from studies 747-213 and 747-214, or other Sponsor studies. The sample size in this study is not calculated based on statistical consideration.

15.3. Safety Analysis

The LTSE Population will be the primary population used for safety analyses.

Safety data, including SAEs, TEAEs, physical examinations, ECGs, vital signs, clinical laboratory assessments, and treatment discontinuations, will be assessed.

The incidence of TEAEs and SAEs will be tabulated by system organ class, preferred term, and severity.

All events of potential hepatic injury, suspected liver-related clinical outcomes, and potential renal injury that occur after administration of the first dose of the investigational product will be reviewed and adjudicated by independent adjudication committees (Section 14.3).

Laboratory parameters and vital signs will be summarized (including Hy's law) using descriptive statistics at baseline (defined as the last assessment performed before the first dose of investigational product in Study 977-311) and at each scheduled post-baseline visit in Study 977-311. The change from baseline will also be summarized. ECGs will be summarized using frequency at each visit. The shift from baseline will also be summarized.

15.3.1. Adverse Events

AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided. The incidence of TEAEs will be tabulated by system organ class and preferred term and by severity and relationship to treatment. Summaries of TEAEs leading to investigational product discontinuation and SAEs will be provided.

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

15.3.2. Clinical Laboratory Evaluations

Laboratory parameters and vital signs will be summarized using descriptive statistics at baseline (defined as the last assessment performed before the first dose of investigational product in Study 977-311) and at each scheduled postbaseline visit. The change from baseline will also be summarized. ECGs will be summarized 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 to assess changes in laboratory values from baseline (Day 1) to each evaluation through Month 60 (EOS) or ET.

15.4. Efficacy Analyses

The LTSE Population will be the population used for the efficacy analyses. Baseline is defined as the last assessment performed before the first dose of investigational product in Study 977311, unless otherwise specified.

The efficacy endpoint at post-baseline site visits includes:

- Response rate of ≥40% reduction from baseline and normalization rates of ALP
- Normalization rates of GGT, ALT, AST, total and conjugated bilirubin
- Change from baseline in GGT, ALT, ALP, AST, and total and conjugated bilirubin
- Percentage of subjects with ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline
- Change from baseline in noninvasive markers of liver fibrosis, including liver stiffness measured by TE and ELF score
- Change from baseline in the GLOBE, UK-PBC, and MELD scores

All continuous and categorical efficacy endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.

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

15.5. Exploratory Analyses

[redacted]

– MELD score ≥15

[redacted]

- Time to first occurrence of each individual component of the composite event endpoint.

All continuous and categorical exploratory endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.

Kaplan-Meier (KM) estimates will be calculated for all time to event endpoints. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve".

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

15.6. PK, PD and PK/PD Analyses

The PK Population will be the primary population used for the PK analyses. The PD population will be the primary population for PD analyses. For PK/PD analyses, subjects in both the PK population and the PD population for the PD endpoint of interest will be included in the analysis. [redacted] will be summarized using descriptive statistics at each scheduled post-baseline visit. PK parameter estimates may be determined for OCA and BZF and their metabolites using a population approach and reported separately. PK analyses reported in the clinical study report (CSR) will consist of individual subject listings and descriptive summary tables of concentrations of OCA and BZF and their metabolites. Change from baseline and percent change from baseline in [redacted] will be calculated by timepoint and reported in individual listings and descriptive summary tables. PK/PD analyses may consist of scatter plots with correlation analysis and additional analyses if warranted by the data.

15.7. 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 completely random. No data will be imputed.

15.8. 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 with 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.

Investigators and site coordinators are trained on different aspects of the web-based EDC system and completion of the eCRF. Data Management also creates instructional material (such as eCRF Completion Guidelines), which is made available to the study sites.

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

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

15.9. Data Monitoring Committee

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

The DMC will have oversight over the study conduct as defined by the 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 but at least every 6 months 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 reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, AEs leading to early withdrawal of investigational product, and hepatic adjudication results. 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.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1. 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, 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 subject visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

16.2. 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.

17. 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 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 16.2 for more details regarding the audit process.

18. ETHICS

18.1. 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. 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.

18.2. 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.

18.3. 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.

18.4. 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/ 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.

19. 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 at 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.

19.1. 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.

19.2. 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.

19.3. 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

19.4. Ethics Review (IRB/IEC)

Please see Section 18.1 for the Investigator's responsibilities regarding ethics review.

19.5. 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.

20. PUBLICATION POLICY

The Sponsor intends to publish the results of all 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, Clinical Trials Information System): 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. 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 B. SUMMARY OF CHANGES: PROTOCOL 977-311 VERSION 2.0 (DATED 18 NOV 2024)

The following is a summary of key changes made to Protocol 977-311 Version 2.0:

- Addition of Day 2 Visit to allow for eligibility laboratory results from Day 1 to be reviewed before dispensing investigational product.
- Updated Patient Reported Outcomes (PROs), key inclusion/exclusion verbiage, and overdose language to align with the other fixed-dose combination (FDC) Phase 3 study and provide additional guidance to Investigators.
- Study Objectives updated to align with recent changes to the hepatic charter.
- Added independent review of potential acute kidney injury events.
- Reduced the burden of sample collection by removing assessment of selected pharmacodynamic markers past one year of study treatment.

The text deleted from Protocol Version 1.0 is crossed out and revised text in Version 2.0 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 2.0 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.

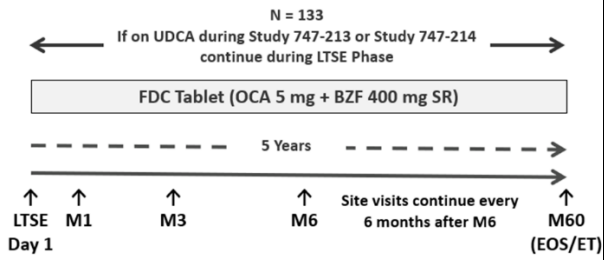
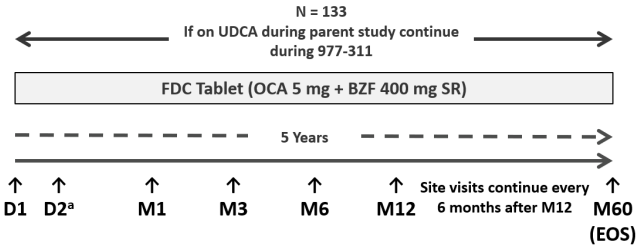
Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
GLOBAL	… from Study 747-213 and Study 747-124… …parent study~~, 747-213 or 747-214~~… *And similar changes throughout protocol.*	…from Study 747-213 and Study 747-124 **(or other eligible Sponsor studies)**… **…**parent study**…** *And similar changes throughout protocol.*	References specifically to Studies 747-213 and 747-214 were clarified to refer to only "parent study" or note other eligible parent studies to leave opportunity for study to be used as LTSE for other parent studies.
GLOBAL	*Addition*	The following study visits were added throughout the protocol: **Day 2, Month 12**	The Day 2 Visit was added to allow for eligibility laboratory results from Day 1 to be reviewed before dispensing investigational product. Month 12 Visit was added to act as a final visit requiring ELF, biomarkers of [redacted] and homeostasis, and [redacted]

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
			[redacted]
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.**	Update of company information.
Investigators Agreement	I have received and read the current version of the Investigator's Brochures (IBs) for obeticholic acid (OCA) and the fixed-dose combination (FDC) (OCA and bezafibrate [BZF]) and this Protocol 977-311. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected subjects according to this protocol. I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.	I have received and read the current version of the Investigator's Brochures (IBs) for obeticholic acid (OCA) and the fixed-dose combination (FDC) (OCA and bezafibrate [BZF]) and this Protocol 977-311. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA/**BZF FDC** to selected subjects according to this protocol. I understand that all information concerning OCA/**BZF FDC** supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms (CRF), and any other preclinical and clinical data provided by the Sponsor.	Clarification
Study Personnel Contact Information	Primary Contact: Direct: [redacted]	Primary Contact: Direct: [redacted]	Update
Synopsis (Studied Period)	~~Estimated~~ date first subject enrolled: ~~Q2~~ 2024	**Actual** date first subject enrolled: **July** 2024	To reflect current study status.
Synopsis (Efficacy Objectives) & 6.2 Efficacy Objectives	To assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following:	To assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following:	Objectives were reclassified from exploratory/additional objectives to efficacy ([redacted]

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	[redacted]	• Biochemical disease markers, including ALP, GGT, ALT, AST, and total and conjugated bilirubin • **ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline** • **Noninvasive assessments of liver fibrosis (transient elastography [TE], enhanced liver fibrosis [ELF] score)** • **Disease severity scores (GLOBE, UK-PBC, and model of end-stage liver disease [MELD])**	[redacted] and from efficacy to exploratory [redacted] now exploratory since only collected up to [redacted]
Synopsis (Exploratory Objectives) & 6.3 Exploratory Objectives	~~Additional~~ Objectives: To assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following: [redacted]	**Exploratory** Objectives: To assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following: [redacted]	Objectives were reclassified from exploratory/additional to efficacy objectives [redacted] and from efficacy to exploratory [redacted] now exploratory since only collected up to [redacted] removed to align with other FDC Phase 3 study and to reduce subject burden.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	[redacted] ~~– MELD score ≥15~~ [redacted]	[redacted] – MELD score ≥15 [redacted]	Duplicate clinical outcomes objective removed. Other clinical outcomes objectives updated to align with recent updates to the adjudication charter.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	[redacted] – MELD score ≥15 [redacted]	[redacted]	
Synopsis (Methodology) & 7.1.1 Methodology	All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits). All subjects should continue their pre-study dose of ursodeoxycholic acid (UDCA) throughout study participation. After the Day 1, Month 1, Month 3, and Month ~~6~~ visits, subsequent in-clinic study visits will occur every 6	**Eligible subjects from other Sponsor studies may also transition to Study 977-311.** All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits) **starting on Day 2**. All subjects should continue their pre-	Clarifications per global changes described above.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	months for the assessment of safety, tolerability, efficacy, PK, and PD.	study dose of ursodeoxycholic acid (UDCA) throughout study participation. After the Day 1, **Day 2,** Month 1, Month 3, **Month 6,** and Month **12** visits, subsequent in-clinic study visits will occur every 6 months for the assessment of safety, tolerability, efficacy, PK, and PD.	
Synopsis (Study Design Diagram) & 7.1.2 Study Design Diagram		 **[a] The Day 2 Visit can be either a virtual or onsite visit. It will be scheduled on Day 2 to Day 7 of the study depending on when laboratory results are available and reviewed. Subjects can elect to pickup IP onsite (onsite Day 2 visit) or have it shipped directly to them (virtual Day 2 visit). For subjects that have IP shipped, the Day 2 virtual visit should be scheduled once the subject receives IP.**	Figure updated to reflect global changes (reference to parent studies and addition of Day 2 and Month 12 visits) described above.
Synopsis (Diagnosis and Main Criteria for Inclusion) & 8.2 Subject Inclusion Criteria	27. All subjects with PBC who participated and are actively taking investigational product in Study 747-213 or Study 747-214 are eligible to enroll in this study (977-311). • Subjects on a drug holiday within the previous ~~45~~ days due to unresolved treatment emergent adverse events (TEAEs) or serious adverse events (SAEs) in ~~studies 747-213 or 747-214~~	28. All subjects with PBC who participated and are actively taking investigational product in Study 747-213 or Study 747-214 **(or other Sponsor studies)** are eligible to enroll in this study (977-311). • Subjects on a drug holiday within the previous **60** days due to unresolved treatment emergent adverse events (TEAEs) or serious adverse events (SAEs) in **the parent study**	Clarifications Duration updated from 45-60 days to allow ample time for resolution prior to rollover into the LTSE.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	should discuss eligibility for rolling over to this study with the Sponsor Medical Monitor.	should discuss eligibility for rolling over to this study with the Sponsor Medical Monitor.	
Synopsis (Diagnosis and Main Criteria for Inclusion) & 8.2 Subject Inclusion Criteria	29. 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 at least ~~14 days or 5 half-lives, whichever is longer,~~ after the last dose of investigational product. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from exposure to investigational medicinal products. … • 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. 30. Male subjects who are sexually active with female partners of childbearing potential must	2. 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 at least **30 days** after the last dose of investigational product. Highly effective methods of contraception per the Clinical Trials Facilitation and Coordination Group guidelines are those that alone or in combination results in a failure rate of less than 1% per year when used consistently and correctly. These highly effective contraception methods avoid the potential embryofetal risks from exposure to investigational medicinal products. **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 **30** days 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. 3. Male subjects who are sexually active with female partners of childbearing potential must agree to use a condom with spermicide and to use	30 days is a conservative timeframe recommended by the following Clinical Trials Coordination Group Guidance, "In case of women of childbearing potential, a minimum of one menstruation cycle (30 days/1 month)… should be awaited after the relevant systemic exposure to the medicinal product has ended." Thirty days is longer than 5 half-lives of OCA, also making it an appropriate timeframe. Other clarifications.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	agree to use a condom with spermicide and to use 1 other approved method of highly effective contraception from the initiation of the study and until at least 90 days after the last dose of investigational product as listed in Inclusion Criterion #2.	**(or have their partner use)** 1 other approved method of highly effective contraception from the initiation of the study and until at least 90 days after the last dose of investigational product as listed in Inclusion Criterion #2.	
Synopsis (Key Exclusion Criteria) & 8.3 Subject Exclusion Criteria	2. Clinical complications of PBC including: • ~~History of liver transplant 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. Any history or presence in the last 30 days, before rolling over to this study, of any one of the following decompensating events: … • Biochemical evidence of hepatic impairment, decompensation, or injury including at least one of the following: • Total bilirubin >~~3 mg/dL (>51.3 µmol/L)~~ • International normalized ratio (INR) >1.7 • Albumin <3.5 g/dL • MELD >12 • ALT >5x ULN … • Hepatorenal syndrome (type I or II) or serum creatinine >1.5 mg/dL (135 µmol/L) or estimated glomerular filtration rate (eGFR) ≤60 mL/min from the last lab	2. Clinical complications of PBC including: • **Prior liver transplantation** 3. Any history or presence in the last 30 days, before rolling over to this study, of any one of the following decompensating events: … • Biochemical evidence of hepatic impairment, decompensation, or injury including at least one of the following: – Total bilirubin >**ULN** – International normalized ratio (INR) >1.7 – Albumin <3.5 g/dL – MELD >12 – ALT >5x ULN … • Hepatorenal syndrome (type I or II) or serum creatinine >1.5 mg/dL (135 µmol/L) or estimated glomerular filtration rate (eGFR) <60 mL/min from the last lab assessment/visit in **parent study**, before transitioning to Study 977-311 …	Verbiage updated to align text with other FDC Phase 3 study. Corrections.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	assessment/visit in ~~Study 747-213 or Study 747-214~~, before transitioning to Study 977-311 … ~~6. History of or current gallbladder diseases with or without cholelithiasis and symptoms~~ ~~7.History 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 …	6. **Evidence or history of cholelithiasis or choledocholithiasis unless documented cholecystectomy. Gallbladder polyps if >5 mm in diameter** 7. **History of chronic pancreatitis or recurrent acute pancreatitis – defined as at least 2 episodes of acute pancreatitis, with symptoms resolving between each episode** 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 …	
Synopsis (Hepatic and Renal Event Adjudication) *Similar changes made in:*14.3 Hepatic and Renal Event Adjudication, &15.3 Safety Analysis	Hepatic Adjudication: All ~~potential~~ events of hepatic injury ~~and~~ suspected liver-related clinical outcomes that occur after administration of the first dose of investigational product will be adjudicated ~~in all enrolled subjects. Potential events of hepatic injury will be reviewed~~ by ~~the~~ independent ~~Hepatic Safety Adjudication Committee (HSAC), and all deaths and suspected liver-related outcomes will~~ be adjudicated ~~by the independent Hepatic Outcomes Committee (HOC).~~	Hepatic **and Renal Event** Adjudication: All events of **potential** hepatic injury**,** suspected liver-related clinical outcomes**, and potential renal injury** that occur after administration of the first dose of investigational product will be **reviewed and** adjudicated by independent **and blinded adjudication committees, depending on event type.** **Each adjudication committee has a charter that documents the reporting of events by the study site, definition of the potential events to** be adjudicated**, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.**	Added review of potential acute kidney injury events.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
Synopsis (Duration of Treatment)	The total duration of Study 977-311 per subject will be a maximum of 60 months~~. Time spent in the LTSE Phase from their previous protocol will not count toward their 60 months in Study 977-311.~~	The total duration of Study 977-311 per subject will be a maximum of 60 months **from day of study entry. The end of study is defined as the date of the last visit of the last subject.**	Clarification.
Synopsis (Analysis Populations) & 15.1 Analysis Populations	LTSE Population: The LTSE Population will include all subjects who receive at least 1 dose of the FDC tablet~~.~~ Pharmacokinetic Population: The PK Population will include all subjects in LTSE Population who receive the FDC tablet and have a PK sample(s) 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 the FDC tablet **in Study 977-311.** Pharmacokinetic Population: The PK Population will include all subjects in LTSE Population who receive the FDC tablet **in Study 977-311** and have a PK sample(s) without any major protocol deviations that could potentially affect plasma exposure.	Clarification since future studies that may roll into this LTSE study may include the FDC tablet as well.
Synopsis (Analysis Populations) & 15.1 Analysis Populations	*Added new text*	**Pharmacodynamic Population: The PD Population will include all subjects with a baseline assessment and at least 1 on-treatment assessment without any major protocol deviations that could potentially affect results.**	Clarified the population to be used for analysis of Pharmacodynamic markers as this population may be different from the PK population.
Synopsis (Safety Analyses) & 15.3 Safety Analysis	Laboratory parameters and vital signs will be summarized (including Hy's law) using descriptive statistics at baseline (defined as ~~Day 1 of~~ Study 977-311) and at each scheduled post-baseline visit in Study 977-311.	Laboratory parameters and vital signs will be summarized (including Hy's law) using descriptive statistics at baseline (defined as **the last assessment performed before the first dose of investigational product in** Study 977-311) and at each scheduled post-baseline visit in Study 977-311.	Clarification with addition of Day 2 Visit.
Synopsis (Analyses of Efficacy and	[redacted]		Endpoints were reclassified from [redacted] and

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
Exploratory Endpoints) *Similar changes in* 15.4 Efficacy Analyses, & 15.5 Exploratory Analyses	The efficacy endpoint at post-baseline site visits includes: • ~~The response rates of ≥10%, ≥20%, ≥30%, and~~ ≥40% reduction from baseline and normalization rates of ALP • Normalization rates of GGT, ALT, AST, total and conjugated bilirubin • Change from baseline in GGT, ALT, ALP, AST, and total and conjugated bilirubin • ~~Change from baseline in~~ [redacted] The ~~additional~~ endpoints at post-baseline site visits include: [redacted]	**investigational product in** Study 977-311**, unless otherwise specified**. The efficacy endpoint at post-baseline site visits includes: • **Response rate of** ≥40% reduction from baseline and normalization rates of ALP • Normalization rates of GGT, ALT, AST, total and conjugated bilirubin • Change from baseline in GGT, ALT, ALP, AST, and total and conjugated bilirubin • **Percentage of subjects with ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline** • **Change from baseline in noninvasive markers of liver fibrosis, including liver stiffness measured by TE and ELF score** • **Change from baseline in the GLOBE, UK-PBC, and MELD scores** The **exploratory** endpoints at post-baseline site visits include: [redacted]	efficacy and from efficacy to exploratory to reflect changes to study objectives as described above. ALP response rates were simplified since range of normalization of ALP will be explored continuously from baseline per the subsequent endpoint. Duplicate clinical outcomes objective removed. Individual adjudication events collapsed for simplification. Other clinical outcome objectives updated to align with recent updates to the hepatic adjudication charter.

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	[redacted] – ~~MELD score ≥15~~ [redacted] – MELD score ≥15 [redacted]	– MELD score ≥15 [redacted]	

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	[redacted] ~~Time to first occurrence of adjudicated event of MELD score ≥15~~ [redacted]	[redacted] All continuous and categorical **efficacy and exploratory** endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.	

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	[redacted] All continuous and categorical ~~additional~~ endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit.		
Synopsis (PK, PD and PK/PD Analyses)	PK and PK/PD Analyses The PK Population will be the primary population used for the PK analyses ~~and includes those who receive~~ the ~~FDC tablet and have enough quantifiable~~ PK ~~samples without any major protocol deviations that could potentially affect plasma exposure~~. [redacted] will be summarized using descriptive statistics at each scheduled post-baseline visit.	PK**, PD** and PK/PD Analyses The PK Population will be the primary population used for the PK analyses. **The PD population will be** the **primary population for PD analyses. For** PK**/PD analyses, subjects in both the PK population and the PD population for the PD endpoint of interest will be included in the analysis**. [redacted] will be summarized using descriptive statistics at each scheduled post-baseline visit. **Change from baseline and percent**	Clarified the population to be used for analysis of Pharmacodynamic markers as this population may be different from the PK population.

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		change from baseline in [redacted] will be calculated by timepoint and reported in individual listings and descriptive summary tables. PK/PD analyses may consist of scatter plots with correlation analysis and additional analyses if warranted by the data.	
Synopsis (Sample Size Determination) & 15.2 Determination of Sample Size	The sample size in this study is not calculated based on statistical consideration.	**This is an estimation study with no formal hypothesis to be tested. Therefore, sample size is strictly based on number of subjects being captured from studies 747-213 and 747-214, or other sponsor studies.** The sample size in this study is not calculated based on statistical consideration.	Updated in response to request for clarification from Regulatory Agency.
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 4 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, 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, and a Phase 1 absorption, metabolism, and excretion study (Study 977-113) in healthy subjects. Study 747-123 is a ~~recently~~ completed ~~(clinical study report [CSR] is in progress)~~, Phase 1, randomized, controlled study evaluating single-dose escalation of	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 4 studies include a Phase 1 study in healthy subjects (Study 747-123), a Phase 2 study (**Study** 747-213) in subjects with PBC that is being conducted **globally (not including** the US**)**, a Phase 2 **study (Study 747-214) being** conducted **globally (including the** US**)** 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, and a Phase 1 absorption, metabolism, and excretion study **of BZF** (Study 977-113) in healthy subjects. Study 747-123 is a completed, Phase 1, randomized, controlled study evaluating single-dose escalation of BZF given alone, multiple-dose escalation of OCA and BZF given alone and in combination, and the relative	Clarification and update to study statuses.

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	BZF 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 enrolled 132 healthy subjects~~, with planned CSR completion by early 2024~~. Study 747-213 is an ongoing, Phase 2, double-blind, randomized, parallel group study evaluating the efficacy, safety and tolerability of OCA administered in combination with BZF in subjects with PBC who had an inadequate response or who were unable to tolerate UDCA. ~~Although Study 747-213 was withdrawn from IND 63307, it is currently ongoing outside the US.~~ This study has been fully enrolled (75 subjects), with a long-term safety extension (LTSE) currently ongoing. Subjects from Study 747-213 will transition into Study 977 311 once the study is active at their respective sites.	bioavailability of OCA and BZF administered in a fixed dose combination tablet compared to each product administered separately in healthy subjects. This study enrolled 132 healthy subjects. Study 747-213 is an ongoing, Phase 2, double-blind, randomized, parallel group study evaluating the efficacy, safety and tolerability of OCA administered in combination with BZF in subjects with PBC who had an inadequate response or who were unable to tolerate UDCA. This study has been fully enrolled (75 subjects), with a long-term safety extension (LTSE) currently ongoing. Subjects from Study 747-213 will transition into Study 977-311 once the study is active at their respective sites.	
5.4.1 Obeticholic Acid	As of 26 May 202~~3~~, approximately 4~~616~~ 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). … 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 Company Core Data Sheet (CCDS) v.4.0, Ocaliva	As of 26 May 202**4**, approximately 4**851** subjects have received **≥1 dose** of 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). … OCA (Ocaliva) has received marketing authorization in **multiple** 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 Company Core Data Sheet (CCDS) v.**5**.0, Ocaliva is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh (CP) Class B or	Update to more recent exposure data. Clarifications

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	is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh (CP) Class B or C) or a prior decompensation event and in patients with complete biliary obstruction. ~~In the US, p~~er 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:	C) or a prior decompensation event and in patients with complete biliary obstruction. **P**er **the** 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 **accelerated or conditional** approval of Ocaliva included 3 randomized, double-blind, placebo-controlled, multi-center, international studies in subjects with PBC:	
5.4.2 Bezafibrate	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 [redacted] mg of [14C]-bezafibrate capsule(s) containing approximately [redacted] µCi, followed up by a 14-day inpatient evaluation period. All subjects have completed the study and the final CSR is pending.~~ Refer to the latest version of the FDC Investigator's Brochure for additional information regarding the BZF clinical program.	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%). Refer to the latest version of the FDC Investigator's Brochure for additional information regarding the BZF clinical program.	Removed the reference to study 977-113 as the CSR is now complete and information can be found in the current FDC IB.
5.4.3 Obeticholic Acid and	*New section added*	**Results from Phase 2 studies (Studies 747-213 and 747-214) demonstrated that OCA in combination with BZF provides substantial improvements in key biochemical**	Section added to summarize results

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Bezafibrate in Combination		**markers. At Week 12, the greatest reductions in ALP were observed in the OCA + BZF 400 mg treatment groups, with an increase in treatment effect with the addition of OCA compared to BZF 400 mg alone. In Study 747-213, treatment with OCA 5 10 mg + BZF 400 mg SR resulted in least square (LS) mean absolute reduction in ALP of 196.4 U/L (62.3%) compared to a 134.2 U/L (45.1%) reduction in the Placebo + BZF 400 mg SR active comparator arm. In Study 747-214, treatment with OCA 5 mg + BZF 400 mg immediate release (IR) resulted in a LS mean absolute reduction in ALP of 183.1 U/L (61.4%) compared to a 164.2 U/L (54.2%) reduction in the Placebo + BZF 400 mg IR active comparator arm.** **Safety data from Phase 1 Study 747-123 and the first 6 months of Phase 2 Studies 747-213 and 747-214 indicated that OCA + BZF was generally well tolerated. The majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. No SAEs have been reported in Study 747-123. In the first 6 months Study 747-213, three SAEs were reported (hypertension, pruritus, and breast cancer). In the first 6 months of Study 747-214 three SAEs were reported (pneumonia, basal cell carcinoma, and intraductal proliferative breast lesion). No TEAEs leading to death have been reported across the 3 studies.**	from Phase 2 studies.
5.5.1 Rationale for Study Design	*New text added*	**Further, as described above, results from Study 747-213 demonstrated that at Week 12 the greatest reduction in ALP was observed in the OCA 5-10 mg + BZF 400 mg SR treatment group, with a clear increase in treatment effect with the addition of OCA compared to BZF 400 mg SR alone. Similarly, in Study 747-214, at Week 12 the greatest reduction in ALP was observed**	Additional information on Phase 2 studies added to support rationale for design.

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		in the OCA 5 mg + BZF 400 mg IR treatment group, with an increase in treatment effect with the addition of OCA compared to BZF 400 mg IR alone.	
5.5.2.2 Bezafibrate Dose	*New text added*	**In an analysis of the ITT population, in both Study 747-213 (BZF 400 mg SR ± OCA) and Study 747 214 (BZF 400 mg IR ± OCA), BZF 400 mg SR demonstrated ability to lower ALP and total bilirubin and improve tolerability (pruritus) at Month 3. In all instances, regardless of formulation and combination with OCA, BZF 400 mg led to greater reductions in ALP and total bilirubin relative to BZF 100 mg and 200 mg at Month 3. Across all treatment groups and irrespective of OCA or BZF dose or formulation, TEAEs were balanced across both Study 747 213 and Study 747-214. Collectively, the greatest improvement in ALP, total bilirubin, and tolerability was achieved with 400 mg BZF SR.**	Additional information on Phase 2 studies added to support rationale of BZF dose used in FDA tablet.
5.6.1 Benefits	*New bullet added*	**4. Results from Phase 2 clinical studies (747-213 and 747-214) have demonstrated an increased treatment effect with the addition of OCA compared to BZF alone.**	Additional information on Phase 2 studies added to support rationale for design.
5.6.2 Risks (Table 1 – Known and Potential Risk of OCA)	<u>Hepatic Adverse Events</u> 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	<u>Hepatic Adverse Events</u> Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with OCA treatment in PBC patients with decompensated cirrhosis. 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	Clarifications. Updates to Risks based on CCDS v5.0.

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	and failure have continued to be reported in patients with decompensated cirrhosis even when they received the recommended dosage. Per the CCDS ~~v4.0~~, 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.~~	recommended dosage. Per the CCDS **v5.0**, 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. **Ocaliva is also contraindicated in patients with compensated cirrhosis with evidence of portal hypertension (e.g. ascites, gastroesophageal varices, persistent thrombocytopenia).**	
5.6.3 Considerations with the Use of OCA and Bezafibrate 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 BZF and OCA concomitantly, it is expected that the safety experience will be similar to the individual products.	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 BZF and OCA concomitantly **and the Phase 2 study data to date**, it is expected that the safety experience will be similar to the individual products.	Additional information on Phase 2 studies added to support rationale for design.
7.1.3 Schedule of Study Procedures (Table 3 – Schedule of Study Procedures)	*Removed columns:* M60 (EOS~~/ET~~), ~~Unscheduled Visit~~ *The following assessments were removed after the new Month 12 visit:* ~~ELF score,~~ [redacted]	*New columns:* **Day 2, Month 12, ET** *The following assessment was added for Day 1 Visit:* **Virology (HCV/HBsAg)** *The following footnote was added for the ET Visit:* **An ET visit should occur in subjects who withdraw from the study. The ET visit should be completed as near as possible to the subject's last dose of IP. Study**	The Day 2 Visit was added to allow for eligibility laboratory results from Day 1 to be reviewed before dispensing investigational product.

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	Other changes and footnotes were updated to reflect changes in the body of the protocol.	**procedures and assessments are not required if previously completed within 4 weeks of the ET.** *Other changes and footnotes were updated to reflect changes in the body of the protocol.*	Month 12 Visit was added to act as a final visit requiring ELF, [redacted] These PD markers were removed to reduce sample burden after one year on-study.
7.1.4 Study Duration	~~All subjects will be rolled over into Study 977-311 from studies 747-213 and 747-214.~~ The total duration of ~~the~~ 977-311 study per subject will be a maximum of 60 months.	The total duration of **Study** 977-311 study per subject will be a maximum of 60 months **from day of study entry**. **The end of study is defined as the date of the last visit of the last subject.**	Clarifications, including global change described above.
7.4.3 Clinical Criteria for Monitoring for Potential Hepatic Decompensation Events (Table 5 – Clinical Criteria for Monitoring Potential	• ~~[redacted], under evaluation for liver transplant, or listed for transplant~~ • Progression to CP score ≥7 • ~~New onset of any of the following:~~ o Ascites o ~~Hepatic hydrothorax~~ o [redacted] o Variceal ~~bleeding~~	• **Clinical evidence of** [redacted] **defined as** [redacted] • **Evidence of hepatic decompensation** o Progression to CP score ≥7 o Ascites **including hepatic hydrothorax** [redacted]	Updated to reflect disease progression sequentially to reflect the pathophysiology of advancing chronic liver disease.

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Hepatic Decompensation Events and Mandatory Discontinuation of Investigational Product)	○ Jaundice (with total bilirubin >3 mg/dL [>51.3 µmol/L]) ○ MELD ≥15 ○ HCC • Any liver-related event requiring hospitalization and treatment [redacted]	○ [redacted] ○ Variceal **hemorrhage** ○ Jaundice (with total bilirubin >3 mg/dL [>51.3 µmol/L]) ○ MELD ≥15 • HCC [redacted]	
7.4.4.3 Potential Myopathy Evaluation and Monitoring	• At Day 1: Check baseline CK: If >5x ULN ~~then screen fail~~.	• At Day 1/**Day 2**: Check baseline CK: If ≥5x ULN **the Medical Monitor and Sponsor Medical Monitor will determine if the subject can continue in Study 977-311 on a case-by-case basis**.	Added Day 2 and additional clarification regarding study participation.
7.5 Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis	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	Investigational product should ~~also~~ be discontinued in the following instances: 1. Development of choledocholithiasis **2. Development of acute cholecystitis** 3. Presence of any gallbladder polyp >5 mm	Verbiage updated to align text with other FDC Phase 3 study.
7.6 Dosage Adjustment Criteria	Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product should ~~come in for the end of study (EOS) Visit and complete the study.~~	Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product should **be requested to continue with study visits until Month 60/end of study (EOS). Subjects who discontinue investigational product may be requested to come in for an Unscheduled Visit at the discretion of**	Subjects will not attend EOS visit until the end of their study participation. Protocol was updated throughout to have subjects

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		the Investigator depending on the timing of their next scheduled study visit.	who only discontinue IP but continue in study to have an Unscheduled Visit as needed.
8.4 Subject Withdrawal Criteria	Subjects who are discontinued from investigational product ~~during the study will be scheduled for an ET Visit.~~	Subjects who are discontinued from investigational product **should be requested to continue with study visits until Month 60/EOS. Subjects who discontinue investigational product may be requested to come in for an Unscheduled Visit at the discretion of the Investigator depending on the timing of their next scheduled study visit.**	Subjects will not attend EOS visit until the end of their study participation. Protocol was updated throughout to have subjects who only discontinue IP but continue in study to have an Unscheduled Visit as needed.
8.4.1 Reasons for Mandatory Discontinuation of Investigational Product	Investigational product will be discontinued permanently if the subject ~~receives~~ a liver transplant or experiences other potential hepatic decompensation events as defined in Table 5. Subjects should be closely monitored until normalization or stabilization and should continue to return for scheduled study visits for safety follow-up.	Investigational product will be discontinued permanently if the subject **has evaluation, listing, or completion of** a liver transplant or experiences other potential hepatic decompensation events as defined in Table 5. Subjects should be closely monitored until normalization or stabilization and should continue to return for scheduled study visits for safety follow-up.	Verbiage updated to align with language in other FDC Phase 3 study.
8.4.1.2 Pregnancy	*Added new text*	**Subjects who plan to become pregnant after study discontinuation or withdrawal should consult with their study doctor or primary HCP.**	To provide additional guidance about conception post-investigational product

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			discontinuation for female subjects and their HCPs.
8.4.2 Other Reasons for Discontinuation of Investigational Product or Study Termination	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 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 8.3)	The following events are considered appropriate reasons for a subject to **be withdrawn from the study or** discontinue investigational product**. Subjects who discontinue investigational product** are expected to continue in the study until study termination (or at the discretion of the Sponsor). … • The occurrence of clinical or laboratory AEs considered by the Investigator **or Sponsor** to be clinically important • The development of any medical conditions listed in the exclusion criteria that might jeopardize patient safety (Section 8.3)	Clarifications. Not all protocol violations warrant discontinuation of investigational product.
8.4.3 Subject Discontinuation Notification	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.	If a subject is withdrawn from the study early (regardless of the cause), all of the **early termination (ET)** evaluations are to be performed at the time of withdrawal, to the extent possible.	Subjects who leave study completely will have ET visit, rather than EOS.
9.2.8 Drug-Drug Interaction	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	BZF For BZF, caution should be exercised when **coumarin-type** 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	Corrections.

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	has been stabilized. Assessment and dosing regimen of anticoagulants is left up to the Principal Investigator's discretion. 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors: Interaction between fibrates and HMG CoA reductase inhibitors (statins) may vary in nature and intensity depending on the combination of the administered drugs. Due to the risk of rhabdomyolysis, BZF should ~~only be administered together with HMG CoA reductase inhibitors in exceptional cases when strictly indicated~~. Subjects receiving this combination therapy must be fully educated or fully informed carefully of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the first signs of myopathy. This combination therapy must not be used in subjects with predisposing factors for myopathy (impaired renal function, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance, and a high alcohol intake). … 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.	been stabilized. Assessment and dosing regimen of anticoagulants is left up to the Principal Investigator's discretion. 3-hydroxy-3-methylglutaryl coenzyme A (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 **not be administered together with HMG CoA reductase inhibitors**. Subjects receiving this combination therapy must be fully educated or fully informed carefully of the symptoms of myopathy and monitored closely. Combination therapy must be discontinued immediately at the first signs of myopathy. This combination therapy must not be used in subjects with predisposing factors for myopathy (impaired renal function, severe infection, trauma, surgery, disturbances of the hormonal or electrolyte balance, and a high alcohol intake). … Resins: When BZF is used concurrently with cholestyramine or any other resin, an interval of at least **4** hours should be maintained between the 2 drugs, since the absorption of BZF is impaired by cholestyramine.	
9.3 Treatment Compliance	The Investigator should assess the subject's compliance with dosing of investigational product at each study visit after Day ~~1~~.	The Investigator should assess the subject's compliance with dosing of investigational product at each study visit after Day **2**.	Update with addition of Day 2. Subjects will not begin dosing until after Day 1 eligibility labs are

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			reviewed and drug is dispensed.
9.4.2 Blinding	Blinding is not applicable to this single-arm study.	Blinding is not applicable to this **open-label,** single-arm study.	Clarification
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-, which is 311- for this study). The next 6 digits (BBBCCC) represent the unique subject identification (ID).	Subjects will be assigned a unique 10-character identifier (AAA-BBBCCC). The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-, which is 311- for this study). The next 6 digits (BBBCCC) represent the unique subject identification (ID).	Correction. This is not a randomized study.
9.7.2 LTSE Period	All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits). All subjects should continue their prestudy dose of UDCA throughout study participation.	All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits) **starting on Day 2**. All subjects should continue their prestudy dose of UDCA throughout study participation.	Clarification since subjects do not start drug until Day 2 Visit.
9.7.2.1 Day 1	~~LTSE~~ Day 1 [redacted] • Obtain blood samples for the following: – Serum chemistry, hematology, and coagulation; see analytes listed in Table 11. – A dedicated serum sample will be collected and sent to the vendor for laboratory testing and calculation of ELF score	Day 1 [redacted] • Obtain blood samples for the following: – Serum chemistry, hematology, and coagulation; see analytes listed in Table 11. – **Virology: HCV/HBsAg** – A dedicated serum sample will be collected and sent to the vendor for laboratory testing and calculation of ELF score	Correction of error from previous version of protocol. Since PK [redacted]

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	[redacted] … ~~• Subjects need to be in fasting condition for at least 8 hours prior to collection of PK samples.~~ [redacted] ~~• Dispense/administer investigational product~~ • ~~Assess investigational product accountability and compliance~~	[redacted] …	
9.7.2.2 Day 2	*New section added*	**The Day 2 Visit can be either a virtual or onsite visit. The following procedures will be performed as listed in Table 3:** • **Verify inclusion and exclusion criteria for eligibility. The Investigator will review Day 1 eligibility laboratory results. If any laboratory results are out of range, the Medical Monitor and Sponsor Medical Monitor will review and determine an appropriate plan for the subject on a case-by-case basis.** • **Record concomitant medications** • **Assess and record any pretreatment AEs including myopathy evaluation** • **Dispense investigational product for subjects still eligible for study. Subjects can elect to pickup investigational product onsite (onsite Day 2 visit)**	The Day 2 Visit was added to allow for eligibility laboratory results from Day 1 to be reviewed before dispensing investigational product.

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		or have it shipped directly to them (virtual Day 2 visit). For subjects that have investigational product shipped, the Day 2 virtual visit should be scheduled once the subject receives investigational product. • **Administer investigational product for subjects still eligible for study. Subjects who have an onsite Day 2 visit will be administered investigational product onsite. Subjects who have a virtual Day 2 Visit will self-administer investigational product during the virtual visit.** • **Assess investigational product accountability and compliance. For subjects who have a virtual Day 2 Visit and have had investigational product shipped, Investigator to confirm that investigational product was received in good condition, was untampered, and is the correct drug. Date of first investigational product administration should be recorded.** • **Remind subject to fast at least 8 hours prior to next onsite visit**	
9.7.2.3 ~~LTSE~~ Month 1, Month 3, Month 6, and Month 12	~~LTSE~~ Month 1, Month 3, Month 6, ~~Every 6 Months from Month 6, and Month 60 (EOS/ET)~~ • ~~Perform standard 12-lead ECG only at Month 60 (EOS)~~ …	Month 1, Month 3, Month 6**, and Month 12** …	Month 12 Visit was added to act as a final visit requiring ELF, [redacted]

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	[redacted] • Obtain blood samples for the following: – Serum chemistry, hematology, and coagulation; see analytes listed in Table 11 – A dedicated serum sample will be collected and sent to the vendor for laboratory testing and calculation of ELF score [redacted] … [redacted] • Dispense/administer investigational product ~~(not at Month 60)~~ • Assess investigational product accountability and compliance • Remind subject to fast at least 8 hours prior to next ~~dosing~~ visit ~~(not at Month 60)~~	[redacted] • Obtain blood samples for the following: – Serum chemistry, hematology, and coagulation; see analytes listed in Table 11 – A dedicated serum sample will be collected and sent to the vendor for laboratory testing and calculation of ELF score [redacted] … • Dispense/administer investigational product • Assess investigational product accountability and compliance • Remind subject to fast at least 8 hours prior to next visit	[redacted] Assessments were updated as appropriate for the new visits covered by the section.
9.7.2.4 Every 6 Months from Month 12, ET, and Month 60 (EOS)	*New section added*	**The following procedures will be performed as listed in Table 3:**	Section added to include only the assessments

		• **Verify that the subject has fasted for at least 8 hours**  • **Record concomitant medications** • **Assess and record any AEs including myopathy evaluation** • **Perform 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)** • **Perform standard 12-lead ECG only at ET and Month 60 (EOS)** • **Calculations for the following:** – **CP Score/Class (assessment of ascites and hepatic encephalopathy is required). See Section 7.4.4 for additional information regarding CP scoring.** – **MELD Score: to be calculated from serum chemistry and other parameters** – **MRS**	required after the Month 12 visit.

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		[redacted] • **Obtain blood samples for the following:** – **Serum chemistry, hematology, and coagulation; see analytes listed in Table 11** – **Obtain** [redacted] • **Urinalysis** • **Perform a urine-based 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.** • **TE (only if test is available at qualified sites)** • **Dispense/administer investigational product (not at ET or Month 60)** • **Assess investigational product accountability and compliance**	

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
		• **Remind subject to fast at least 8 hours prior to next visit (not at Month 60)**	
9.7.3 Unscheduled/Safety Visit	The Investigator may schedule an Unscheduled/Safety Visit at any time if clinically warranted based on Investigator discretion. A PK sample should be collected if an unscheduled visit occurs due to a safety event. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted ~~as shown in Table 3~~. As appropriate, the Medical Monitor should be contacted.	The Investigator may schedule an Unscheduled/Safety Visit at any time if clinically warranted based on Investigator discretion. **Subjects who discontinue investigational product but continue in the study may be requested to come in for an Unscheduled Visit at the discretion of the Investigator depending on the timing of their next scheduled study visit. These subjects will then be requested to continue with regularly scheduled study visits until Month 60/EOS.** A PK sample should be collected if an unscheduled visit occurs due to a safety event. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted **at the discretion of the Investigator**. As appropriate, the Medical Monitor should be contacted.	Protocol was updated throughout to have subjects who only discontinue IP but continue in study to have an Unscheduled Visit as needed.
11.2 Disease-Specific Symptoms as Assessed by Questionnaires	[redacted]		Removed to align with other FDC Phase 3 study and to reduce subject burden.
13.1 PK Blood Sampling	Subjects need to be in fasting condition for at least 8 hours prior to collection of PK samples. A [redacted] through Month 60 (EOS~~/ET~~)~~.~~	Subjects need to be in fasting condition for at least 8 hours prior to collection of PK samples. [redacted] through Month 60 (EOS**), and the** ET **and/or Unscheduled Visits (if applicable).** [redacted]	Updates made to align with changes to visit schedule. Language indicating that the investigational

<table>
<tr><th>Section</th><th>Original Text (Version 1.0, 25 Jan 2024)</th><th>Revised Text (Version 2.0, 18 Nov 2024)</th><th>Key Change Reasons/ Justification for Change</th></tr>
<tr><td></td><td>~~Subjects should take investigational product with the provided low-fat meal or meal replacement drink.~~

The acceptable windows for sample collection are shown in Table 7.

Table 7: Acceptable Windows for Pharmacokinetic Sample Collection
<table><tr><th>Nominal Sampling Time</th><th>Acceptable Sampling Window</th></tr><tr><td>[redacted]</td><td>30 minutes before dosing</td></tr></table></td><td>sample also must be collected within 7 days of a safety event (e.g., event related to potential hepatic or muscular injury).

The acceptable windows for sample collection on Month 1 through Month 60 Visits are shown in Table 7. There is no window required for the Day 1 Visit as investigational product will not be administered.

Table 7: Acceptable Windows for Pharmacokinetic Sample Collection (Month 1 through Month 60)
<table><tr><th>Nominal Sampling Time</th><th>Acceptable Sampling Window</th></tr><tr><td>[redacted]</td><td>30 minutes ±15 minutes before dosing</td></tr></table></td><td>product to be taken with a low fat meal or meal replacement drink is only relevant for post-dose PK sampling, which is not included in this study. Therefore, the language was removed.

PK samples were added for unscheduled visits if applicable to inform exposure safety analyses.</td></tr>
<tr><td>14.1.1.3 Treatment-Emergent Adverse Events</td><td>A 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.</td><td>A TEAE is any event not present before the initiation of the investigational product in this study or any event already present, which worsens in either severity or frequency following exposure to the investigational product in this study.</td><td>Clarification to specify TEAE is defined as events starting or worsening in this study, not parent study.</td></tr>
<tr><td>14.1.3.1 Severity of Pruritus (as an Adverse Event)</td><td>• 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.</td><td>• 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. If the drug holiday lasts more than 30 days, the subject</td><td>To align with updates to have subjects continue with study visits even if they are discontinued.</td></tr>
</table>

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	• Per Section 8.4.1.1, 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. ~~If the drug holiday lasts more than 2 weeks, the subject should be withdrawn from the study.~~	**should be permanently discontinued from investigational product but requested to continue with study visits until Month 60/EOS.** • Per Section 8.4.1.1, 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.	
14.1.5 Overdose	*New section added*	**An overdose is defined as administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information. When applying this definition, clinical judgement should always be applied (EMA 2017). The event of overdose should be carefully assessed and reported (e.g., intent, exposure, signs, symptoms, and potential confounders). PK sample must be collected. Patient-reported history of overdose must be assessed and documented regarding intent, exposure, and potential co-ingestants.** **Per the CCDS v5.0, in clinical trials, patients with PBC who received OCA 25 mg QD (2.5-times the highest recommended dosage) or 50 mg QD (5-times the highest recommended dosage) experienced a dose-dependent increase in the incidence of hepatic adverse reactions, including elevations in liver biochemical tests (transaminase and bilirubin up to greater than 3x ULN), ascites, jaundice, portal hypertension, and PBC flares.** **While there has been no reported case of overdosage in treatment with BZF, symptomatic and supportive measures should be taken. Because BZF is highly bound to plasma proteins, hemodialysis should not be**	Updated to align with other FDC Phase 3 study and to provide clear investigator guidance.

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		considered. In patients with existing impaired renal function, if dosage recommendations are not followed, overdosage may occur and severe rhabdomyolysis may develop. Administration of BZF must be stopped immediately and renal function must be carefully monitored. **In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.**	
14.1.9 Follow Up of AEs and SAEs	Drug-Induced Liver Injury or Disease Progression All subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. ~~Results from DILI 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 DILI, indicating that liver injury was related to underlying liver disease.~~	Drug-Induced Liver Injury or Disease Progression All subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped.	Correction
14.2.6 Laboratory Assessments (Table 11 – List of Laboratory Scores and Analytes)	Serum chemistry: Albumin, ALP, BUN, creatinine, conjugated (direct) bilirubin, 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)	Serum chemistry: Albumin, ALP, BUN, creatinine, conjugated (direct) bilirubin, 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, free fatty acids, eGFR, CK**, and CrCL**	Corrections

Section	Original Text (Version 1.0, 25 Jan 2024)	Revised Text (Version 2.0, 18 Nov 2024)	Key Change Reasons/ Justification for Change
	bilirubin, free fatty acids, eGFR, ~~and~~ CK	… **Virology** **HCV, HBsAg**	
15 Statistics	An SAP providing details regarding the specific planned analyses will be prepared, finalized, and approved before study ~~database lock~~. The SAP will be prepared as soon as planning for the statistical methods section of the protocol is initiated.	An SAP providing details regarding the specific planned analyses will be prepared, finalized, and approved before **any** study **snapshot**. The SAP will be prepared as soon as planning for the statistical methods section of the protocol is initiated.	Clarification to allow for data cuts not associated with formal database lock.
15.3.2 Clinical Laboratory Evaluations	In addition, shift tables from baseline based on normal ranges will be provided for hematology, coagulation, and serum chemistry to assess changes in laboratory values from baseline to each ~~on-study~~ evaluation.	In addition, shift tables from baseline based on normal ranges will be provided for hematology, coagulation, and serum chemistry to assess changes in laboratory values from baseline **(Day 1)** to each evaluation **through Month 60 (EOS) or ET.**	Clarification
15.6 PK, PD and PK/PD Analyses	15.6. PK and PK/PD Analyses The PK Population will be the primary population used for the PK ~~and~~ PK/PD analyses~~.~~ [redacted] will be summarized using descriptive statistics at each scheduled post-baseline visit. PK parameter estimates ~~will~~ be determined for OCA and BZF and their metabolites using a population approach~~.~~ ~~Non-compartmental analyses may be considered if deemed appropriate~~. PK analyses reported in the CSR will consist of individual subject listings and descriptive summary tables of concentrations of OCA and BZF and their metabolites. ~~PK parameter analyses and PK/PD (i.e., exposure-response) analyses, will be performed using a multiple-study/program-level~~	15.6 PK**, PD** and PK/PD Analyses The PK Population will be the primary population used for the PK **analyses. The PD population will be the primary population for PD analyses. For** PK/PD analyses**, subjects in both the PK population and the PD population for the PD endpoint of interest will be included in the analysis.** [redacted] will be summarized using descriptive statistics at each scheduled post-baseline visit. PK parameter estimates **may** be determined for OCA and BZF and their metabolites using a population approach **and reported separately**. PK analyses reported in the **clinical study report (**CSR**)** will consist of individual subject listings and descriptive summary tables of concentrations of OCA and BZF and	Clarified the population to be used for analysis of Pharmacodynamic markers as this population may be different from the PK population. Other clarifications and consistencies with other sections to the protocol made.

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	~~approach to be described in a Clinical Pharmacology Analysis Plan and may be reported in a Clinical Pharmacology Analysis Report, separate from the CSR~~.	their metabolites. **Change from baseline and percent change from baseline in [redacted] will be calculated by timepoint and reported in individual listings and descriptive summary tables. PK/PD analyses may consist of scatter plots with correlation analysis and additional analyses if warranted by the data**.	
18.4 Subject Confidentiality and Data Protection	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.	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/site number only.	Correction. This is not a randomized study.
20 Publication Policy	• 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.	• Clinical Trial Registries (e.g., www.clinicaltrials.gov, **Clinical Trials Information System**): 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.	Update
21 List of References	*New Reference*	**European Medicines Agency (EMA). Guideline on Good Pharmacovigilance Practices (GVP). Annex I—Definitions (Rev 4). EMA/876333/2011 Rev 4, 22. 2017.**	Updates to match what is used in document.