Clinical Study Protocol 747-304

OBETICHOLIC ACID (OCA)

A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obeticholic Acid in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis

The REVERSE Study

Randomized phase 3 study EValuating the Efficacy and safety of obeticholic acid in subjects with compensated ciRrhosis due to nonalcoholic StEatohepatitis

Version 7.0: 16 June 2021

EudraCT Number: 2017-000474-11

ClinicalTrials.gov Identifier:NCT03439254

Sponsor

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

_____ _____

[redacted]MD Date

[redacted] Clinical Development
Intercept Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-304. 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, electronic case report forms (eCRF), and any other preclinical and clinical data provided by the Sponsor.

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

By my signature below, I hereby attest that I have read, understood, and agreed to abide by all the conditions, instructions, and restrictions contained in Protocol 747-304 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

Emergency Contact Information

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Primary Contact: [redacted], MB ChB
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SAE Reporting Information

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic Acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid; INT-747; DSP-1747

Title of Study:

A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obeticholic Acid in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis

Investigators and/or Study Center(s):

Approximately 300 investigational sites, globally.

Studied Period:

The maximum duration of individual subject participation for this study is approximately 2 years and 9 months, including a Screening Period of up to 12 weeks, an 18-month Double-Blind Phase, and an Open-Label Extension (OLE) expected to last approximately 1 year.

Phase of Development:

Phase 3

Objectives:

Primary Objectives Assessed at the End of the Double-Blind Phase

To evaluate the effects of OCA treatment compared with placebo on:

- Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of nonalcoholic steatohepatitis (NASH) defined as no increase in hepatocellular ballooning or lobular inflammation, using the NASH Clinical Research Network (CRN) scoring system, from Baseline to the end of the Double-Blind Phase

Secondary Objectives Assessed at the End of the Double-Blind Phase

To evaluate the effects of OCA treatment compared with placebo on:

- Resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase
- Resolution of NASH based on pathologist's overall histopathologic interpretation of the presence or absence of definite NASH from Baseline to the end of the Double-Blind Phase
- Histological changes in fibrosis status including: (1) improvement, or (2) no change, from Baseline to the end of the Double-Blind Phase using the NASH CRN scoring system
- Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint):
  - Death (all causes)
  - Liver transplant
  - Model for end-stage liver disease (MELD) score ≥15
  - Worsening of Child-Pugh (CP) score (by at least 2 points)
  - Hospitalization (as defined by a stay of ≥24 hours) for:
    - Variceal bleed

- Hepatic encephalopathy (as defined by a West Haven score of ≥2)
- Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)

– Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)

– Hepatocellular carcinoma (HCC) as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy

[redacted]

Safety Objectives Assessed at the End of the Double-Blind Phase

- To evaluate the safety and tolerability of OCA treatment compared to placebo
- The effect of OCA treatment compared to placebo on the following additional measures and markers:
  - Markers of cardiovascular safety
  - Incidence of adjudicated cardiovascular events
  - Incidence of adjudicated acute kidney injury events (AKI)
  - Incidence of adjudicated events of hepatic injury

Primary Objectives Assessed at the End of the OLE

- To evaluate and summarize the longer-term safety and tolerability of OCA treatment
- To summarize the effects of OCA treatment on the occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint):
  - Death (all cause)
  - Liver transplant
  - MELD score ≥15
  - Worsening of CP score (by at least 2 points)
  - Hospitalization (as defined by a stay of ≥24 hours) for:
    - Variceal bleed
    - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
    - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
  - Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)
  - HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy

Methodology:

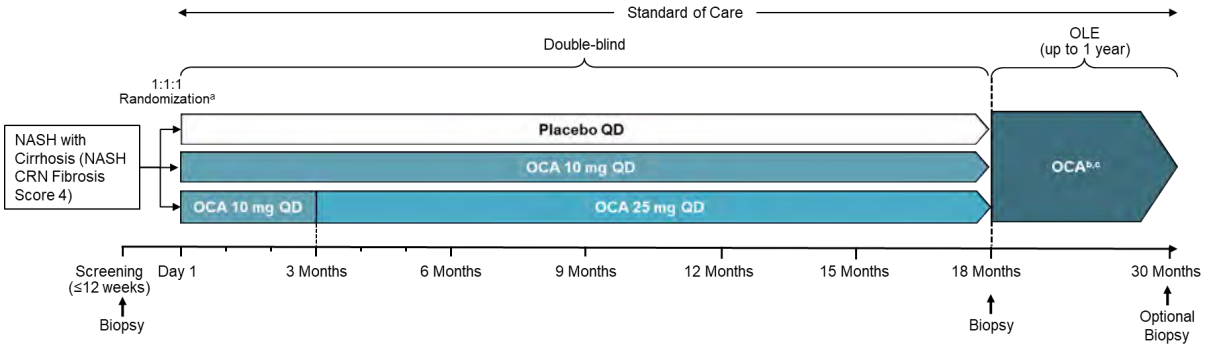
This Phase 3, double-blind, randomized, placebo-controlled, multicenter international study will evaluate the efficacy and safety of OCA in subjects with a biopsy-confirmed diagnosis of cirrhosis (based on a fibrosis score of 4 using the NASH CRN scoring system) due to NASH (determined by central reading of liver histology). Subjects with hepatic decompensation or CP Class B or Class C cirrhosis are excluded. Subjects who progress to CP Class B or Class C during the study will discontinue investigational product but are expected to be followed through to study closure (or at the discretion of the Sponsor).

Double-Blind Phase (18 Months): Subjects will be screened for a period of up to 12 weeks before entering the study. Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with the standard of care. Uptitration will be determined based on the laboratory criteria and safety and tolerability assessments completed prior to Month 3.

Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). Investigational product (ie, OCA or placebo) will be taken orally, with water, once daily. Efficacy, safety, and laboratory assessments will be evaluated at clinical visits at Day 1, monthly for the initial 6 months (Month 1 through Month 6 Visits), Month 9, Month 12, Month 15, and Month 18.

Open-Label Extension (up to 12 Months): Subjects who complete the Double-Blind Month 18 Visit and continue to receive investigational product are eligible to enroll into the OLE. All subjects will receive OCA upon entry into the OLE. Subjects randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). Uptitration will be determined based on the same criteria and assessments as employed in the Double-Blind Phase. Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase; however, they will undergo dummy titration to maintain study blind until all subjects complete the Double-Blind Phase and the database is locked.

Study Design Diagram



CP = Child-Pugh; CRN = clinical research network; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = once daily.

[a] Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with the standard of care.

[b] All subjects will receive OCA upon entry into the OLE: Subjects who received placebo during the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at OLE Month 3). Subjects who received OCA during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase.

[c] During the OLE period, subjects will return for site visits at Months 1, 2, 3, 4, 5, 6, 9, and 12.

Notes:

- Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH (determined by central reading of liver histology) will be enrolled in the study. Subjects with hepatic decompensation or CP Class B or CP Class C cirrhosis are excluded.
- Two screening visit assessments will be performed. Screening Visit 1 will occur no more than 12 weeks prior to Day 1, and Screening Visit 2 will occur at least 4 weeks after Screening Visit 1.
- Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no).
- The study will remain blinded until all subjects complete the Double-Blind Phase and the database is locked. To maintain blinding, all investigational product (placebo and OCA) tablets and bottles will be identical.

Number of Subjects (planned): Approximately 900 subjects will be enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Subjects ≥18 years of age
2. Subjects with a confirmed diagnosis of NASH and a fibrosis score of 4 based upon the NASH CRN scoring system determined by central reading of a liver biopsy obtained no more than 12 months before Day 1.
3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Female subjects are considered as being of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   Effective methods of contraception are listed below:

   – Barrier method ie, (a) condom (male or female) with spermicide or (b) diaphragm with spermicide; or
   – Intrauterine device; or
   – Vasectomy (partner); or
   – Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
   – Abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse)
4. Must provide written informed consent and agree to comply with the study protocol

Exclusion Criteria

Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization.

For alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome), if the Screening Visit 2 value is ≥30% higher than the Screening Visit 1 value and > the upper limit of normal (ULN), then a third measurement must be obtained at an unscheduled visit. Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment:

1. Current or past history of a clinically evident hepatic decompensation event, such as ascites, variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes
2. Current or past history of hepatic function impairment with CP score ≥7 points
3. MELD score >12
4. Hospitalization within 1 year of Day 1 for complications of cirrhosis
5. Documented presence of varices based on prior endoscopy performed within 6 months of Day 1
6. AST ≥5× ULN
   a. If a third serum AST measurement is required, and both Screening Visit 2 and unscheduled visit AST values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment
7. ALT ≥5× ULN
   a. If a third serum ALT measurement is required, and both Screening Visit 2 and unscheduled visit ALT values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment

8. Calculated creatinine clearance <60 mL/min using Cockcroft-Gault method
9. Platelet count ≤100 000/mm^3
10. Total bilirubin >2 mg/dL (except for subjects with an established diagnosis of Gilbert's syndrome, if hemoglobin and reticulocyte count are within normal range and conjugated bilirubin is <1.5× ULN)
    a. If a third serum total bilirubin measurement is required (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome), and both Screening Visit 2 and unscheduled visit values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment
11. Conjugated bilirubin ≥1.5x ULN
12. Albumin <3.5 g/dL
13. International normalized ratio (INR) ≥1.7
14. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before Day 1 (significant alcohol consumption is defined as more than 2 units/day for females and more than 4 units/day for males, on average)
15. Prior (at any point) or planned (during the study period) ileal resection, or prior (within 5 years before Screening) or planned (during the study period) bariatric surgery (eg, gastric bands, gastroplasty, Roux-en-Y gastric bypass)
16. Inability to safely undergo a liver biopsy
17. History of biliary diversion
18. Evidence of other known forms of chronic liver disease including:
    - Positive test result at Screening for hepatitis B surface antigen
    - Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or confirmed history of a positive HCV RNA test result(s) except for subjects with evidence of spontaneous HCV eradication (defined as positive HCV antibodies at Screening, no history of positive HCV RNA result, and documentation that no anti-HCV therapy has been received)
    - Primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome
    - Alcoholic liver disease
    - Wilson disease, hemochromatosis, or iron overload
    - Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion)
    - Prior known or suspected drug-induced liver injury within 5 years before Day 1
    - Known or suspected HCC
19. History of liver transplant or current placement on a liver transplant waiting list
20. Hemoglobin A1c (HbA1c) ≥9.5% within 90 days before Day 1
21. Low-density lipoprotein (LDL) cholesterol ≥190 mg/dL and already on a stable dose of LDL-lowering medication for ≥30 days
22. LDL cholesterol <50 mg/dL in subjects not on LDL-lowering medication
23. Known positivity for human immunodeficiency virus infection
24. Subjects with recent history (within 1 year of Day 1) of significant atherosclerotic cardiovascular disease (ASCVD; myocardial infarction, unstable angina, acute coronary syndrome, cerebrovascular accident [stroke], cerebrovascular ischemia, transient ischemic attack, or peripheral vascular disease requiring intervention). Such subjects may be identified by different means, including, but not limited to, an abnormal 12-lead electrocardiogram (ECG), a history or planned cardiovascular intervention such as coronary revascularization (eg, percutaneous coronary intervention or coronary artery bypass graft), coronary angioplasty, stenting, carotid atherectomy, or placement of a cardiac pacemaker or defibrillator
    - Controlled hypertension without other recent manifestations of significant ASCVD and placement of cardiac pacemaker or defibrillator for reasons other than ASCVD (eg, for treatment of atrial fibrillation subsequent to nodal ablation) is not exclusionary

25. Current acute cholecystitis or acute biliary obstruction
26. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign carcinomas)
27. Known substance abuse in the year before Screening
28. Chronic use (≥12 months) of drugs historically associated with drug-induced NAFLD within the 5 years before Day 1 (eg, amiodarone, methotrexate, systemic glucocorticoids [unless used at physiologic replacement doses for the treatment of adrenal insufficiency], tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids [except for testosterone preparations used at physiologic replacement doses for the treatment of documented/confirmed hypogonadism], valproic acid, and other known hepatotoxins).
29. Pregnancy, planned pregnancy, potential for pregnancy (ie, unwillingness to use effective birth control during the study), or current or planned breast feeding
30. Participated in a clinical research study and received any active investigational product being evaluated for the treatment of diabetes, weight loss, or NASH in the 6 months before Day 1
31. Concurrent participation in any other interventional clinical trial.
32. Received any investigational product from Screening to Day 1, within 30 days before Day 1, or within 5 half-lives of the compound (whichever was longer) before Day 1
33. Previous exposure to OCA within 12 months of Day 1
34. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study, is uncertain
35. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
36. Any other condition that, in the opinion of the Investigator, might confound the results, or would impede compliance or hinder completion of the study
37. Alkaline phosphatase (ALP) ≥1.5x ULN
38. History of known or suspected hypersensitivity to any ingredient in human albumin preparations (at US sites where [redacted] will be conducted)

Liver Histology and Event Adjudication and Data Monitoring Committee Oversight:

Central Reading of Liver Histology: All biopsy assessments will be performed centrally, including assessments of biopsies to determine study eligibility. Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN scoring system must be confirmed for study eligibility. For each biopsy, fibrosis will be graded in accordance with the NASH CRN scoring system (Kleiner 2005).

Biopsy samples will be assessed for quantitative collagen in a subset of subjects as an exploratory objective.

Any extra biopsy tissue may undergo additional histological evaluations such as alpha-smooth muscle actin or bile acid transporter analysis.

Event Adjudication: Potential liver-related clinical outcomes, and potential events of hepatic injury, AKI, and major adverse cardiovascular events (MACE), deaths, and hospitalizations (depending on the cause) that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 4 committees that are responsible for adjudicating events are as follows:

- Cardiovascular Adjudication Committee: Adjudicates all potential MACE (including all deaths) and hospitalizations (depending on the cause)
- Hepatic Outcomes Committee: Adjudicates all deaths and potential liver-related clinical outcomes
- Hepatic Safety Adjudication Committee (HSAC): Adjudicates all potential events of hepatic injury
- Renal Adjudication Committee: Adjudicates all potential events of AKI

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.

Specific details of the events that will be adjudicated by the Cardiovascular Adjudication Committee, Hepatic Outcomes Committee, HSAC, and Renal Adjudication Committee 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.

DMC Oversight: An independent DMC will review all safety and efficacy data resulting from the study at periodic intervals. In addition, PK exposure data will be available, if needed. The DMC will include hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), drug-induced liver injury (DILI) expert(s) and statistician(s); they will not be involved in the study as Investigators, adjudication committee members, or consultants. All members will have considerable experience with clinical study conduct and DMCs.

Investigational Product, Dosage and Mode of Administration:

OCA tablet, 10 mg or 25 mg, once daily, oral administration

Reference Therapy or Investigational Product, Dosage and Mode of Administration:

Placebo tablet, matched in size and appearance to OCA tablets, oral administration

Duration of Treatment:

The maximum duration of treatment is approximately 2 years and 6 months, including an 18-month Double-Blind Phase, and an OLE expected to last approximately 1 year.

Criteria for Evaluation

Analyses Variables	Endpoint Assessments
Primary Objectives Assessed at the End of the Double-Blind Phase	
Histological improvement in fibrosis using NASH CRN scoring system	Improvement in fibrosis by at least 1 stage with no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase
Secondary Objectives Assessed at the End of the Double-Blind Phase	
Resolution of NASH	No fatty liver disease or fatty liver disease (simple or isolated steatosis) without steatohepatitis AND a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase
	NASH resolution based on pathologist's overall histopathologic interpretation of the presence or absence of definite NASH from Baseline to the end of the Double-Blind Phase
Histological change in fibrosis (improvement and no change)	Change in NASH CRN scoring system from Baseline to the end of the Double-Blind Phase
Clinical outcomes	Occurrence of any of the following adjudicated events: death (all cause); liver transplant; MELD score ≥15; worsening of CP score by at least 2 points; hospitalization (as defined by a stay of ≥24 hours) for variceal bleed, HE (as defined by a West Haven score of ≥2) or SBP (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis); HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy
[redacted]	

[redacted]

Safety Objectives Assessed at the End of the Double-Blind Phase	
Safety and tolerability	TEAEs, adverse events of special interest (including cardiovascular, pruritus, renal, urinary tracts stones including nephrolithiasis, gallbladder/gallstones-related pancreatitis, hepatic, dyslipidemia and hyperglycemia/new-onset diabetes mellitus AEs), ECGs, vital signs, pruritus VAS, and clinical laboratory assessments (including lipid profile changes)

Markers of cardiovascular safety	Lipoproteins (LDL, HDL, VLDL, ApoB, ApoA-1, ApoE, Lp[a]), total cholesterol, triglycerides, PCSK9, cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, and SCORE)
Adjudicated cardiovascular events for cardiovascular outcomes assessment	Incidence of cardiovascular events including core MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure, and arrhythmias). Other events potentially related to adverse cardiovascular outcomes as defined in Appendix E and included in the CAC charter will be sent to the CAC for adjudication.
Adjudicated events of AKI	Incidence of adjudicated events of AKI
Adjudicated events of hepatic injury	Incidence of adjudicated events of hepatic injury
Primary Objectives Assessed at the End of the OLE	
Analyses Variables	**Assessments**
OLE safety and tolerability	TEAEs adverse events of special interest (including cardiovascular, pruritus, renal, urinary tracts stones including nephrolithiasis, gallbladder/gallstones-related pancreatitis, hepatic, dyslipidemia and hyperglycemia/new-onset diabetes mellitus AEs), ECGs, vital signs, pruritus VAS, and clinical laboratory assessments (including lipid profile changes)
Clinical outcomes	Occurrence of any of the following adjudicated events: death (all cause); liver transplant; MELD score ≥15; worsening of CP score by at least 2 points; hospitalization (as defined by a stay of ≥24 hours) for variceal bleed, HE (as defined by a West Haven score of ≥2), or SBP (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis); HCC confirmed by 2 complementary imaging modalities unless already confirmed by biopsy
[redacted]	

AKI = acute kidney injury; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoA-1 = apolipoprotein A1; ApoB = apolipoprotein B; ApoE = apolipoprotein E; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; aPTT = partial thromboplastin time; ASCVD = atherosclerotic cardiovascular disease; C4 = 7α-hydroxy-4-cholesten-3-one; CAC = Cardiovascular Adjudication Committee; CK-18-M30 = cytokeratin-18 neoepitope; M30; CK-18-M65 = cytokeratin-18 neoepitope M65; CLDQ = Chronic Liver Disease Questionnaire; CRN = Clinical Research Network; CP = Child-Pugh; DSI = disease severity index; ECG = electrocardiogram; ELF = Enhanced Liver Fibrosis; EQ-5D-5L

[redacted]

[redacted] HCC = hepatocellular carcinoma; HDL = high-density lipoprotein; HE = hepatic encephalopathy; HOMA-β = homeostatic model assessment–beta cell; HOMA-IR = homeostatic model assessment – insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; INR = international normalized ratio; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); MACE = major adverse cardiovascular events; MELD = model for end-stage liver disease; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD activity score; NASH = nonalcoholic steatohepatitis; NFS = NAFLD fibrosis score; OCA = obeticholic acid; OLE = open-label extension; PCA = percent collagen area; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; SAE = serious adverse event; SBP = spontaneous bacterial peritonitis; SCORE = systemic coronary risk evaluation; TE = transient elastography; TEAE = treatment-emergent adverse event; TNF-α = tumor necrosis factor-α; US = United States; VAS = visual analog scale; VLDL = very low-density lipoprotein; WPAI = Work Productivity and Activity Index.

Statistical Methods:

A detailed statistical analysis plan, providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees. A separate clinical pharmacology analysis plan will be prepared, providing details of PK analysis methods and parameter estimation. PK/PD analytical methods will be detailed in a separate modeling and simulations plan, and all results will be documented separate from the clinical study report. Details about these specific planned analyses will be prepared and approved by the Sponsor or its designees prior to study database lock.

Enrollment and Randomization

Approximately 900 subjects will be enrolled and randomized into the study in a 1:1:1 ratio to OCA 10 mg, OCA 10 mg → 25 mg, or placebo arms. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no).

Analysis Populations

Intent-to-Treat (ITT) Population:

The ITT Population will include all randomized subjects. The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.

Modified Intent-to-Treat (mITT) Population:

The mITT Population will include all ITT subjects except those who are not eligible to dose titrate due to safety or tolerability reasons. Treatment assignment will be based on the randomized treatment.

Per Protocol (PP) Population:

The PP Population will include all mITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusions. Treatment assignment will be based on the randomized treatment.

Safety Population:

The Safety Population will include all randomized subjects who receive at least 1 dose of investigational product (OCA or placebo). The Safety Population will be the primary population used for safety analyses. Treatment assignment will be based on the treatment actually received.

[redacted]

Efficacy Analyses

For the comparison of the primary efficacy endpoint, a Cochran Mantel Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] will be used. The overall type I error will be controlled at 0.05 for the primary analysis

Primary efficacy hypothesis testing will be based on the ITT population. Supportive analyses of the primary endpoint will be conducted using the mITT and PP population.

The primary efficacy analysis will test the following hypotheses:

- H_{01}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system from Baseline to the end of the Double-Blind Phase is equal between placebo and OCA 10 to 25 mg titration.
- H_{11}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is different between placebo and OCA 10 to 25 mg titration.
- H_{02}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is equal between placebo and OCA 10 mg.
- H_{12}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is different between placebo and OCA 10 mg.

The type 1 error for the primary efficacy analysis will be controlled at 0.05. For the comparison of the primary and secondary efficacy endpoints, a Cochran–Mantel– Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] will be used.

Analyses of the clinical outcomes composite endpoint will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo, as listed under the secondary objectives. Only adjudicated events will be included in analyses. Subjects with none of these events will be censored at the date of last contact. For the analysis of time to first occurrence of adjudicated events, in addition to the CMH test statistics, a log rank test stratified by the randomization stratification factor (presence of type 2 diabetes at enrollment [yes/no]) will be used. Kaplan-Meier estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group.

[redacted]

[redacted]

Safety Analyses

Safety evaluations will comprise treatment-emergent AEs, AEs of special interest (including cardiovascular, pruritus, renal, urinary tract stones including nephrolithiasis, gallbladder/gallstone-related, pancreatitis, hepatic, dyslipidemia, and hyperglycemia/new-onset diabetes mellitus AEs), adjudicated hepatic safety events, adjudicated cardiovascular events, adjudicated AKI events, vital signs, electrocardiograms (ECGs), pruritus VAS, and clinical laboratory results.

[redacted]

Safety Analyses (OLE)

Safety evaluations conducted during the Double-Blind Phase will also be conducted for the OLE. For quantitative parameters including, but not limited to, vital signs, ECG, and clinical laboratory results, changes from double-blind baseline value and OLE baseline value will be presented. Analyses based on the double-blind baseline will be performed using the treatment actually received in the Double-Blind Phase. Analyses based on the OLE baseline will be based on the treatment actually received in the OLE Phase.

Efficacy Analyses (OLE)

The occurrence of all-cause mortality and liver-related clinical outcomes will be summarized. For additional exploratory analyses, please refer to SAP for more details.

Sample Size Justification

A sample size of 300 subjects per group will provide at least 90% power to detect a statistically significant treatment difference of 10% between OCA 25 mg and placebo groups based on a Chi-square test with 2-sided type I error at 0.05 level, assuming a responder rate of 10% in the placebo group. As there was no previous study performed using the same endpoint in this disease, the assumption was determined based on data from literature, and results from the Farnesoid X receptor Ligand OCA in Nonalcoholic Steatohepatitis Treatment (FLINT) study and Study 747-303.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
A1AT	alpha-1-antitrypsin
ADA	American Diabetes Association
AE	adverse event
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoA-1	apolipoprotein A-1
ApoB	apolipoprotein B
ApoE	apolipoprotein E
APRI	aspartate aminotransferase to platelet ratio index
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BA	biliary atresia
BAS	bile acid sequestrants
β-hCG	beta human chorionic gonadotropin
BLM	baseline measurement
BMI	body mass index
BUN	blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
CAC	Cardiovascular Adjudication Committee
CDCA	chenodeoxycholic acid
CHI3L1	chitinase 3-like protein 1
CI	confidence interval
CK-18-M30	cytokeratin-18 neoepitope M30
CK-18-M65	cytokeratin-18 neoepitope M65
CLDQ	Chronic Liver Disease Questionnaire
Col1a1	Collagen 1a1
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRN	Clinical Research Network
CS	clinically significant

Abbreviation or Specialist Term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CP	Child-Pugh
CPMP	Committee for Medicinal Products for Human Use
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSI	disease severity index
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
ELF	Enhanced Liver Fibrosis
Emax	maximum effect
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor-19
FIB-4	Fibrosis-4
FLINT	Farnesoid X receptor Ligand OCA in Nonalcoholic Steatohepatitis Treatment
FRS	Framingham Risk Score
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
glyco-OCA	glycine conjugate of obeticholic acid
HA	hyaluronic acid
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCP	health care provider
HCV	hepatitis C virus
HDL	high-density lipoprotein

Abbreviation or Specialist Term	Explanation
HE	hepatic encephalopathy
HOMA-β	homeostatic model assessment –beta cell
HOMA-IR	homeostatic model assessment –insulin resistance
HSAC	Hepatic Safety Adjudication Committee
hs-CRP	high-sensitivity C-reactive protein
HSC	hepatic stellate cells
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
[redacted]	[redacted]
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-Treat
KM	Kaplan-Meier
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
LS	least-squares
MACE	major adverse cardiovascular events
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP-1	monocyte chemoattractant protein-1
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
mITT	modified intent-to-treat
MRE	magnetic resonance elastography
MW	molecular weight
NAFLD	nonalcoholic fatty liver disease
NAS	nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
NCS	not clinically significant

Abbreviation or Specialist Term	Explanation
NFS	nonalcoholic fatty liver disease fibrosis score
OCA	obeticholic acid
OLE	open-label extension
P3NP	procollagen III amino terminal peptide
PBC	primary biliary cholangitis
PCA	percent collagen area
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per protocol
PT	prothrombin time
PTT	partial thromboplastin time
QTcF	QT interval corrected by the Fridericia's formula
RNA	ribonucleic acid
RTSM	Randomization and trial supply management
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SCORE	systemic coronary risk evaluation
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAA	thioacetamide
tauro-OCA	taurine conjugate of obeticholic acid
TE	transient elastography
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinase 1
[redacted]	[redacted]
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VLDL	very low-density lipoprotein
WPAI	Work Productivity and Activity Index

5. INTRODUCTION

5.1. Overview of Nonalcoholic Steatohepatitis and Obeticholic Acid

Nonalcoholic fatty liver disease (NAFLD) is considered to be a hepatic manifestation of metabolic syndrome, a cluster of closely related clinical features linked to visceral obesity and characterized by insulin resistance, dyslipidemia, and hypertension. NAFLD is the most common cause of chronic liver disease in the western hemisphere. As the prevalence of obesity and metabolic syndrome rises in the industrial world, NAFLD is expected to rise in parallel. NAFLD is thought to be represented by a spectrum of histologically-defined diseases, which progresses from simple steatosis to nonalcoholic steatohepatitis (NASH). Up to one-third of NAFLD patients go on to develop NASH, which is characterized by hepatocellular injury, inflammation, and progressive fibrosis potentially leading to cirrhosis. As opposed to simple steatosis, NASH is associated with significant morbidity and progression that, if left untreated, can progress to advanced fibrosis, cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver-related death (Vernon 2011). Of all the histologic features of NASH, fibrosis is considered the strongest predictor of adverse clinical outcomes, including liver-related death (Younossi 2011, Ekstedt 2015).

Despite the seriousness of the disease, especially when advanced fibrosis/cirrhosis is present, there are currently no approved pharmacologic treatments. The current treatment strategy for NASH patients with cirrhosis becomes largely supportive, focused primarily on managing complications and, as a last resort, liver transplant. It is therefore critical to develop effective therapies that can reverse fibrosis or prevent the progression of fibrosis to cirrhosis, with the goal of reducing complications secondary to cirrhosis ultimately improving quality of life and liver-transplant-free survival.

In view of the serious nature of the disease, the increasing prevalence, the complications that arise from the disease, and the unmet medical need, approved therapy for NASH is warranted.

Obeticholic acid (OCA) is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary bile acid chenodeoxycholic acid (CDCA), the natural human FXR ligand.

OCA's potent FXR agonist effects make it an attractive novel therapeutic agent for NASH due to its multiple FXR-mediated effects, including prevention and reversal of liver fibrosis, anti-inflammatory effects in liver and vasculature, and hepatocyte protection against bile acid-induced cytotoxicity. Specifically, nonclinical studies have shown several potentially beneficial properties of FXR agonism in NASH and cirrhosis (Adorini 2012, Mudaliar 2013).

5.2. Nonclinical Experience with OCA

Non-clinical studies clarifying the anti-inflammatory, anti-fibrotic and anti-cirrhotic mechanisms underlying OCA's effect in NASH include the following:

- In mice, OCA has been shown to alleviate key histologic hallmarks of NASH in high-fat/high-cholesterol diet-induced and biopsy-confirmed disease as reflected by improvements in nonalcoholic fatty liver disease activity score (NAS), steatosis, ballooning and immunohistochemical markers of fibrosis (eg, collagen 1a1 [Col1a1])

and inflammation (eg, galectin 3; Roth 2017). These effects were associated with regulation of FXR target genes within the gut-liver axis and improvements in genes involved in monocyte recruitment and fibrosis (eg, monocyte chemoattractant protein-1 [MCP-1], Col1a1, collagen type III alpha 1 chain, membrane palmitoylated protein 2, tissue inhibitor of metalloproteinase 2). These findings further confirm the benefits of FXR agonism by OCA in a rodent model of NASH.

- Hepatic fibrosis ultimately progresses to cirrhosis. While it is difficult to induce cirrhosis by simple high fat feeding, this stage can be readily induced in rodents by the application of thioacetamide (TAA). Importantly, therapeutic effects have been demonstrated when OCA was administered concurrently or following established cirrhosis within the rat TAA model (Verbeke 2016). These benefits were associated with: (1) functional hepatic improvements such as a reduction in portal pressure through reduced intrahepatic vascular resistance, and (2) a decreased expression of pro-fibrotic cytokines (transforming growth factor β, connective tissue growth factor, and platelet derived growth factor) and markers of hepatic cell turn-over by blunting effects of pro-inflammatory cytokines (MCP-1).
- To dissect out the contribution of individual cell types, in vitro studies interrogated the potential for direct effects of OCA upon isolated hepatic stellate cells (HSCs), Kupffer cells, hepatocytes, and liver sinusoidal endothelial cells. Collectively, these findings suggest that the improvements manifest via indirect effects on immune activation and hepatic cell turn-over and are linked to a decrease in nuclear factor kappa-light-chain-enhancer of activated B cell activation and cytokines promoting fibrosis and inflammation within the liver parenchyma (Verbeke 2016). These effects do not appear to be due to a direct effect upon HSCs (Fickert 2009, Verbeke 2016).
- Although not formally addressed in a cirrhotic model, interactions between the intestinal mucosal barrier and liver (the "gut-liver axis") are recognized as important contributors to the clinical pathogenesis of NASH (van Best 2015). Under healthy conditions, the intestinal mucosal barrier is the first line of defense against antigens and inflammatory mediators escaping from gut mucosal immune surveillance. Disruption results in bacterial translocation to the extra-intestinal space, activating the immune system and triggering further hepatic inflammation and damage. In animal models (Garcia-Tsao 1995) and human cirrhosis, bacterial translocation is a prelude to hepatic decompensation, further liver impairment, and, ultimately, organ failure. In preclinical models, these effects are attenuated following OCA administration. For example, OCA inhibits gastrointestinal inflammation and preserves intestinal barrier function in models of inflammatory bowel diseases, upregulating expression of anti-bacterial genes and inhibiting bacterial translocation (Gadaleta 2011). In the bile duct ligation model, OCA treatment improves ileal barrier function by attenuating intestinal inflammation and reducing bacterial translocation, a key driver in the pathogenesis and complications of liver cirrhosis (Verbeke 2015).

In summary, there is strong rationale to advance OCA for the treatment of NASH based on its FXR-mediated hepatoprotective properties.

5.3. Clinical Experience with Obeticholic Acid

OCA (Ocaliva) has received marketing authorization in the United States, Europe, Canada, and several other countries for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. OCA is currently being developed for the treatment of multiple chronic nonviral liver diseases, including NASH with fibrosis, NASH with cirrhosis, primary sclerosing cholangitis, and biliary atresia.

The clinical development program for OCA in subjects with NAFLD or NASH includes data from the following 6 completed studies:

- Study 747-203: A proof-of-concept, Phase 2 study in subjects with type 2 diabetes and presumed NAFLD to evaluate the effects of OCA on insulin sensitivity (Mudaliar 2013).
- FXR Ligand OCA in NASH Treatment (FLINT): A Phase 2 study conducted by the National Institute of Diabetes and Digestive and Kidney Diseases and the NASH Clinical Research Network (CRN) to evaluate the efficacy and safety of OCA in the treatment of NASH (Neuschwander-Tetri 2015).
- Study D8602001: A Phase 2 study conducted by Intercept's Asian development partner (Sumitomo Dainippon Pharma Co., Ltd) to evaluate the efficacy and safety of 3 doses of OCA versus placebo in NASH.
- Study 747-209: A Phase 2, double-blind, randomized, placebo-controlled, multicenter study evaluating the effect of OCA, and the subsequent addition of statin therapy, on lipoprotein metabolism in subjects with NASH with fibrosis stage 1 to 4, but no evidence of hepatic decompensation.
- Study 747-117: A Phase 1, double-blind, randomized, placebo-controlled study evaluating the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of OCA in subjects with NASH fibrosis.
- Study 747-118: A Phase 1, single-center, double-blind, randomized study evaluating the safety, pharmacokinetics, and pharmacodynamics of OCA in healthy subjects and subjects with compensated Child-Pugh (CP) Class A cirrhosis due to NASH.
  - Including a 747-118 hepatic PK substudy in subjects with cirrhosis due to NASH.

Study 747-203 showed improved insulin sensitivity in subjects with type 2 diabetes and NAFLD, demonstrating the clinical relevance of the FXR agonist pathway and supporting the potential of OCA to treat NAFLD and/or NASH. With the exception of weight loss, OCA 25 mg appeared to be at least as effective as OCA 50 mg for the majority of endpoints evaluated. Pruritus (including generalized pruritus) in Study 747-203 occurred at a comparable incidence in OCA-treated and placebo-treated subjects with NAFLD; the incidence was approximately 9% to 10% between placebo and the highest OCA dose (50 mg). No subject from Study 747-203 withdrew from the study due to pruritus.

The FLINT study demonstrated that OCA 25 mg was superior to placebo in improving not only the key histologic features important in the underlying pathophysiology of the disease

(inflammation, ballooning, and steatosis), but notably also fibrosis (35% OCA versus 19% placebo; p = 0.004). Across all fibrosis change categories (fibrosis improvement of ≥1 stage of fibrosis, ≥2 stages of fibrosis or resolution of fibrosis), a greater percentage of OCA-treated subjects were responders compared to placebo. Importantly, a significantly greater percentage of subjects in the OCA group (17%) showed fibrosis resolution after 72 weeks of treatment compared to placebo (5%). In addition, although the numbers were small (likely due to the limited 72-week treatment period), fewer OCA-treated subjects (2%) progressed to cirrhosis compared to placebo (5%). OCA treatment was also associated with improvement in markers of hepatocellular injury and some cardiometabolic features, including weight and systolic blood pressure.

Low-density lipoprotein cholesterol (LDLc) demonstrated a modest but significant increase in subjects treated with OCA compared to placebo; however, this increase was reversed and LDLc cholesterol returned to below baseline levels in subjects who initiated statin therapy. The general adverse event (AE) profile was similar between the OCA 25 mg and placebo groups, with the exception of pruritus. Pruritus occurred more frequently in the OCA-treated subjects (23% OCA versus 6% placebo), led to 1 discontinuation, and was generally mild and moderate in severity. Otherwise, pruritus was well managed with the use of antipruritic medications and treatment interruption.

Study D8602001 demonstrated a dose-dependent increase in the percentage of OCA-treated subjects compared to placebo subjects who achieved the primary endpoint (p = 0.053, not significant). The 40-mg OCA dose group achieved statistical significance for the primary endpoint compared to placebo (p = 0.0496). Dose-dependent trends not reaching statistical significance were also observed for several other pre-specified histologic endpoints, including the proportion of subjects with steatosis and inflammation improvement, ballooning resolution, and NASH resolution. In the completer analysis, similar dose-dependent effects were observed, with 51% of patients in the 40-mg dose group compared to 22% in the placebo group meeting the primary endpoint (p = 0.0061). With the exception of dose-dependent pruritus, OCA appeared to be generally safe and well tolerated. The number of pruritus-associated treatment discontinuations were 0, 0, 2, and 5 subjects in the placebo, 10-mg, 20-mg, and 40-mg OCA groups, respectively. Changes in lipid parameters were directionally similar to those observed in NASH subjects in the FLINT study. No other meaningful differences in the rate of AEs between the OCA and placebo groups were noted.

Study 747-209 further evaluated the effect of OCA and atorvastatin treatment on LDLc metabolism in subjects with NASH and liver fibrosis to better characterize the lipid profile changes observed in the FLINT study, as well as their management. Subjects with biopsy-confirmed NASH and fibrosis received placebo or OCA 5 mg, 10 mg, or 25 mg once daily, for up to 4 weeks. Subjects then initiated concurrent treatment with atorvastatin 10 mg once daily, and titrated to 20 mg once daily at Week 8 based on tolerability. At Week 4, prior to initiation of statin treatment, subjects experienced an approximately 20% to 25% increase in LDLc concentrations across all OCA groups. By Week 8, atorvastatin treatment effectively lowered LDLc to below baseline levels across all treatment groups. Together, these study results suggest that the risk of increases in LDLc with OCA use can generally be managed by statin use. Pruritus was the most common AE and was dose dependent. Two subjects discontinued the study due to pruritus.

Study 117 demonstrated that the PK profile of OCA in subjects with NASH fibrosis was consistent with what has been observed in healthy subjects and largely reflective of enterohepatic recirculation with exposure proportional to dose. Treatment with OCA 10 mg or 25 mg once daily for 12 weeks was found to be safe and well tolerated in NASH subjects with fibrosis (including fibrosis stage 1 through stage 4). The PD assessments demonstrated FXR activation and positive trends for select markers of fibrosis, inflammation, apoptosis, and liver function.

Study 747-118 demonstrated that the safety profile of 10 mg and 25 mg doses of OCA in subjects with compensated CP Class A cirrhosis due to NASH was similar to the safety observed in healthy subjects, supporting their use in longer term efficacy studies. The hepatic PK substudy demonstrated that OCA 25 mg was safe and generally well tolerated, showing improvements in the levels of liver biochemistry markers associated with hepatocellular injury when administered for 28 days to subjects with CP Class A cirrhosis due to NASH, consistent with results from the double blind period.

The following studies evaluating OCA for the treatment of NASH are currently ongoing:

- The clinical outcome portion of Study 747-303.

A complete description of the OCA clinical development program is provided in the Investigator's Brochure.

5.4. Rationale for Study Design and Dose for Investigational Product

5.4.1. Rationale for Study Design

NASH is a serious, chronic liver disease with a large unmet medical need and no approved therapies. Patients with cirrhosis in the spectrum of NASH disease continuum represent the highest unmet medical need and are at the greatest risk of disease progression. NASH has become one of the leading causes of liver transplant (Wong 2020, Younossi 2020), highlighting the need for development of effective therapies that may improve steatohepatitis and fibrosis, potentially delaying liver transplant or death. As fibrosis has been consistently shown to be the strongest predictor of adverse clinical outcomes, including liver-related death, it is critical to prevent further progression of fibrosis and preferably reverse fibrosis. Results from FLINT and the 18-month interim analysis of Study 747-303 have demonstrated that OCA has robust anti-fibrotic effects and improves underlying disease activity and steatohepatitis in NASH subjects with fibrosis at the 18-month assessment. Study 747-304 will evaluate efficacy (based on histological improvement in fibrosis) and safety of OCA in NASH subjects with compensated cirrhosis (defined by a NASH Clinical Research Network [CRN] score of 4), and CP score <7.

5.4.2. Rationale for Placebo Control Group

The use of a randomized placebo control group added to established standard of care, including lifestyle modification counseling, provides the best scientific evidence of efficacy and safety. The use of a placebo control provides a concurrent comparator group, accounting for not only a placebo effect but a standard of care effect. As there is no approved or proven pharmacologic therapy for NASH, using a placebo for comparative purposes is justified.

5.4.3. Rationale for Obeticholic Acid Doses and Duration

In addition to placebo, two dosing regimens of OCA will be evaluated in this study: (1) Titration regimen (OCA 10 mg → 25 mg) in which OCA will be initiated at a dose of 10 mg once daily followed by uptitration to 25 mg once daily at Month 3; and (2) OCA 10 mg once daily for the entire duration of the study.

This dose titration was selected based upon the known mechanism of FXR and on clinical experience in completed Phase 2 studies in subjects with NAFLD (747-203) and NASH (FLINT), as well as a clinical pharmacology study in subjects with hepatic impairment (Study 747-103).

FXR is a nuclear receptor that senses bile acids and regulates their intracellular levels in hepatocytes. FXR activation leads to the reduction of intracellular bile acid levels by increasing the export of bile acids from cells, thereby decreasing bile acid uptake and bile acid synthesis. After 12 weeks of dosing OCA, FXR activation has been shown to reduce systemic bile acid levels while maintaining relatively low OCA levels in the total bile acid pool (<2%).

Study 747-203, a 6-week study that evaluated the efficacy and safety of OCA 25 mg, OCA 50 mg, and placebo in 64 subjects with type 2 diabetes mellitus and NAFLD, demonstrated that both OCA 25 mg and 50 mg doses were similarly efficacious in improving insulin sensitivity as well as markers of fibrosis such as Enhanced Liver Fibrosis (ELF).

The efficacy and safety of OCA 25 mg was also evaluated in the FLINT study in which patients with NASH fibrosis were treated for a period of 72 weeks. In this study, OCA-treated patients showed significant improvements in histologic parameters, including improvements in features of steatohepatitis, improvement of fibrosis, and resolution of NASH. In both studies, OCA 25 mg was well tolerated with pruritus being the most common treatment-emergent adverse event (TEAE) in FLINT (23% OCA vs 6% placebo). In summary, the OCA 25 mg dose has demonstrated significant histologic improvement in patients with NASH fibrosis while being well tolerated, and has therefore been selected for further evaluation in the population with cirrhosis who has not reached CP score ≥7.

The dedicated hepatic impairment study (747-103) using OCA 10 mg has shown only 10% increase in the systemic concentrations of total OCA in subjects with CP Class A compared to that of healthy subjects.

Therefore, the dose of OCA 10 mg will be administered for 3 months to support the lowering of bile acid levels in CP Class A subjects. After 3 months, titration of OCA 25 mg administration is introduced to provide clinically proven beneficial doses. Study 747-209 evaluated a range of doses from 5 mg to 25 mg in subjects with NASH and fibrosis, including subjects with compensated cirrhosis. In this study, treatment of NASH subjects with compensated cirrhosis with up to 25 mg OCA was found to be safe and well tolerated, and the AE profile of cirrhotic subjects was not different from that of precirrhotic subjects. Guidelines for subjects who progress beyond CP Class A are provided in Section 7.4.

In addition to the titration dosing regimen, an arm evaluating OCA 10 mg once daily will also be evaluated. While OCA 25 mg once daily was well-tolerated overall, there was an increased incidence of mostly mild or moderate pruritus in OCA-treated subjects compared to placebo-treated subjects in the FLINT and 747-209 studies. Pruritus was also the most common AE associated with OCA in PBC studies, and has been shown to be dose related, warranting

evaluation of lower doses as a potential strategy to improve tolerability. Phase 2 and Phase 3 studies evaluating OCA for the treatment of PBC have shown that the incidence and severity of pruritus with OCA treatment can be mitigated with lower OCA doses. Therefore, based on the therapeutic effect of 10 mg in PBC and to evaluate potential attenuation of effect of OCA on pruritus and serum lipid levels, a lower dose of 10 mg daily will be evaluated in this study in addition to the titration dosing regimen.

Rationale for Treatment Duration of 18 Months

The natural history of NASH with liver fibrosis shows that both progression and regression of liver fibrosis are slow processes that may take years to develop as well as to improve. A systematic review and meta-analysis of paired-biopsy studies has shown that a 1-stage change in fibrosis occurs over a median of 7.1 years in patients with NASH (Singh 2015). Regression of fibrosis in established NASH cirrhosis is expected to take even longer (Cheung 2019). To date, no clinical trial in subjects with NASH cirrhosis has demonstrated efficacy with respect to reversal of cirrhosis and there are no approved treatment options for NASH cirrhosis.

As presented above, OCA has shown robust anti-fibrotic effects based on histologic endpoints in pre-cirrhotic NASH subjects with liver fibrosis. A treatment duration of 12 months was initially selected for the placebo-controlled portion of this study based on non-histological data (using serum biomarkers of fibrosis observed in Study 747-203 and FLINT). However, the effects of OCA on liver histology at earlier time points, including 12 months, had not been assessed. The preliminary results of the 18-month interim analysis from Study 747-303 showed that OCA 25 mg was superior to placebo, demonstrating histological improvement of NASH fibrosis without worsening of NASH with an effect size of ~11% over 18 months of treatment (Younossi 2019). However, the results also highlighted the slow process of regression of liver fibrosis and the potential challenges of demonstrating efficacy in regression of liver fibrosis within a finite time period. Based on the above considerations, the duration of treatment in the Double-Blind Phase has been extended to 18 months.

5.5. Summary of Known Potential Risks with Investigational Product

The rate of progression and risk of hepatic decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk. Investigators should inform participating subjects of known and anticipated risks associated with OCA treatment and prompt them to communicate with the Investigators in the event of any adverse experiences.

Post-Marketing Cases of Liver Injury in PBC

In post-marketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in PBC subjects with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCA was dosed more frequently than the recommended starting dosage of 5 mg once weekly (ie, off-label use). Subjects who died due to hepatic complications generally had decompensated cirrhosis prior to treatment and were started on OCA 5 mg QD, which is 7-fold greater than the once weekly starting regimen in this population and considered to be a medication error.

Based on a comprehensive review in 2017 of both existing and new clinical information, including more than 1300 patient-years of exposure and subjects with advanced disease, multiple analyses confirm lack of hepatotoxicity at the current recommended doses of OCA. The existing

post-marketing evidence at that time was considered insufficient to confirm a causal relationship between exposure to OCA and the occurrence of hepatic decompensation and/or death. The majority of cases reported were for advanced PBC patients receiving doses inconsistent with dosing instructions in the label. Even in these cases, there is no clear evidence that the higher than recommended dosing frequency of OCA led to adverse outcomes.

PBC is a chronic progressive liver disease, ultimately progressing to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, liver transplant, and/or death. Given that hepatic decompensation events are part of the natural history of PBC and patients with end stage disease are particularly vulnerable, it is often not possible to distinguish on a case level the hypothesized drug effects from the natural history of the disease.

As a result, a boxed warning was added to the labeling in 2018 providing additional guidance on patient management for patients with decompensated cirrhosis as well as stronger dosing guidelines.

A new label, approved on 01 June 2021, states that in the US, OCA is now contraindicated in PBC subjects with compensated cirrhosis with evidence of portal hypertension after a Newly Identified Safety Signal evaluation.

Clinical Study Experience

Liver-related events

Systemic and hepatic concentrations of OCA increase significantly in patients with moderate to severe hepatic impairment. In PBC clinical studies, a dose-response relationship was observed for the occurrence of liver-related adverse reactions with OCA, including jaundice, worsening ascites, and PBC flare with dosages of OCA 10 mg to 50 mg once daily. Most events occurred at a dose up to 5-fold higher (50 mg) than the maximum recommended marketed dose (10 mg).

Clinically relevant increases in AST, ALT, or conjugated bilirubin (markers of liver injury) were rarely seen at the intended clinical doses of 5 mg or 10 mg. Elevated liver enzymes were observed in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies; however, these elevations were only considered to be of clinical concern at the maximum dose of 250 mg daily. Cases of hepatic decompensation cases have also occurred in PBC. The majority of the cases were considered not related or unlikely related to investigational product by the Investigator. In general, subjects who experienced hepatic decompensation either entered the study with more advanced disease, or for those studies where subjects started earlier in disease progression, events of hepatic decompensation generally occurred at least 1 year after the initiation of treatment or on higher doses.

In a pooled analysis of 3 completed placebo-controlled clinical trials in subjects with primarily early-stage PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant hepatic adverse reactions and isolated elevations in liver biochemical tests per 100 patient exposure years 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.

Analyses of liver-related safety information from NASH subjects treated with OCA demonstrate an overall hepatic safety profile consistent with PBC. There is no evidence to indicate a consistent, dose-dependent worsening of liver biochemistries at doses up to 25 mg, including

ALT, AST or bilirubin. Modest increases in alkaline phosphatase (ALP) levels have occurred following treatment with OCA; however, ALP levels were generally within upper limits of normal. ALP elevations are generally not associated with a rise in gamma-glutamyl transferase (GGT), suggesting that these changes are unlikely to be due to cholestatic liver injury.

In NASH clinical trials 9 cases of hepatic decompensation have been reported as SUSARs, 1 of which resulted in death. The signs of hepatic decompensation included death due to a hepatic event; MELD score ≥15; liver transplant; ascites; or a serious adverse event (SAE) of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.

Of these events, one was considered unlikely related to OCA and 6 were considered possibly related to blinded treatment. The remaining events were considered possibly related to treatment and concerned subjects receiving daily OCA 40 mg. One case describes a subject with an event of DILI, and a second case describes a subject with events of ascites and pruritus. In the case with ascites and pruritus, treatment was discontinued. Both subjects recovered from the events.

Key hepatic findings in NASH subjects include the following:

- In completed NASH clinical studies, cumulative on-study incidence rates for hepatic AEs and corresponding hazard ratios indicate that the rates of hepatic SAEs are not different across OCA and placebo groups. Although more events occurred in the OCA 25 mg group (6 [1%] subjects) than in the OCA 10 mg group (2 [<1%] subjects) or placebo group (2 [<1%] subjects), expert reviewers did not identify sufficient evidence supporting a consistent pattern of liver injury, and notably, the vast majority of cases were associated with confounding concomitant medications or severe intercurrent illness.
- Given that the liver is the primary site of action for OCA safety and efficacy, liver concentrations for total OCA were predicted for subjects with hepatic impairment based on Child-Pugh Class score. A 1.1-fold increase in liver OCA exposure is predicted in subjects with mild hepatic impairment (Child-Pugh Class A); however, a 1.5- and 1.7-fold increase in liver concentrations of OCA are predicted for Child Pugh Class B and C respectively, when compared to that of healthy subjects (Edwards 2016). In a hepatic impairment study (747-118) in NASH subjects with compensated liver cirrhosis (Child-Pugh Class A), plasma exposure was approximately 4- to 10-fold higher, and liver exposure was approximately 2-fold higher as compared to NASH subjects with liver fibrosis. OCA has not been evaluated in NASH subjects with decompensated cirrhosis (Child-Pugh Class B and Child-Pugh Class C).

Pruritus

Pruritus is an expected adverse event associated with OCA, particularly in subjects with cholestatic liver diseases such as PBC where pruritus is a common symptom of the disease. In PBC clinical studies, the incidence of pruritus was 68% for OCA-treated subjects compared with 40% in placebo-treated subjects. The majority of events have been reported as mild to moderate in severity and infrequently resulted in early discontinuation. The majority of subject's experiencing pruritus did not require an intervention for pruritus. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease.

Pruritus has also been observed in subjects with NASH. Across the three, long-term, double-blind, placebo-controlled studies in subjects with liver fibrosis due to NASH (747-303, FLINT, and D8602001), the incidence of pruritus TEAEs was dose dependent and higher in the OCA 25 mg group, as compared to the OCA 10 mg and placebo groups. The majority of pruritus TEAEs were mild to moderate in severity. The incidence of severe pruritus TEAEs was low, but higher in the OCA 25 mg group, as compared to the OCA 10 mg and placebo groups. The incidence of new or worsening pruritus TEAEs was highest early in the course of treatment (ie, first 3 months) and subsequently decreased over time. Consistent with the PBC experience, pruritus in subjects with NASH appeared to be manageable with temporary interruption of OCA treatment and the use of antipruritic medications.

Lipids

In subjects with NASH (FLINT), compared to placebo, treatment with OCA was associated with statistically significant elevations in the mean total serum cholesterol and LDLc levels, and a decrease in the mean HDL, which remained within normal limits. These changes developed within the first 12-week time point after beginning of treatment, decreased over time after Week 12, and returned to baseline levels when OCA treatment was withdrawn.

Withdrawal of OCA treatment reversed the OCA-induced LDLc increase in all groups, including subjects who were not on statins (Neuschwander-Tetri 2015). In Study 747-209, subjects with NASH and dyslipidemia received placebo or OCA 5mg, 10 mg, and 25 mg once daily, for up to 4 weeks. Subjects then initiated concurrent treatment with 10 mg atorvastatin once daily titrated to 20 mg once daily based on tolerability. At Week 4, subjects experienced approximately 20% to 25% increases in LDLc particles across all OCA groups. By Week 8, atorvastatin treatment effectively lowered LDLc to below baseline levels across all OCA groups compared to patients not on a statin.

Together, the small magnitude of OCA mediated cholesterol and LDL changes, coupled with their reversibility upon cessation of OCA treatment and/or responsiveness to statin-initiation, suggest that this risk can be managed by statins as needed.

Glycemic Changes

In NASH clinical studies, treatment with OCA was associated with a generally modest and transient rise in glycemic parameters (fasting plasma glucose, fasting serum insulin, and hemoglobin A1c (HbA1c), a well-established marker of long-term glycemic control) that occurred early (ie, within the first 3 months) and attenuated, returning to levels similar to placebo after approximately 6 months of treatment.

5.5.1. Risk/Benefit Profile of OCA in Subjects with NASH

An independent data monitoring committee (DMC) has performed detailed reviews of individual subject and aggregate data from both the Phase 3 clinical outcomes study in subjects with PBC (Study 747-302) and the Phase 3 pivotal studies in subjects with NASH fibrosis (Study 747-303) and NASH cirrhosis (Study 747-304) on a quarterly basis, in an unblinded fashion, and in closed sessions (without the Sponsor's participation).

Following a request from the FDA, an ad hoc DMC review was held, and the DMC recommended that:

- For subjects in Study 747-303, investigational product should be interrupted in subjects who experience symptomatic cholelithiasis and/or cholecystitis.

In a subsequent DMC review, the DMC recommended that:

- For subjects in Study 747-303, investigational product should be permanently discontinued in subjects diagnosed with acute pancreatitis.

The Sponsor decided to implement the DMC recommendations across the NASH program.

In summary, based on the robust efficacy of OCA observed in PBC and NASH clinical studies, including improvements in liver biochemistry, fibrosis, and key histological features of NASH, as well as the overall safety profile of OCA (in >2300 healthy subjects and subjects with chronic liver diseases), the benefit-risk profile is favorable.

Refer to the Investigator's Brochure for additional information regarding the known potential risks with the investigational product.

5.6. Importance of Monitoring of Disease Progression

NASH is a chronic, progressive liver disease with variable rates of progression to cirrhosis and hepatic decompensation, although both may occur rapidly in certain patients. Subjects with NASH cirrhosis have accentuated risks relative to subjects with non-cirrhotic NASH and can transition abruptly from a clinically compensated state to decompensated cirrhosis, with the manifestations of portal hypertension and impaired synthetic function that characterize end-stage liver disease. Subjects with NASH cirrhosis must, therefore, be closely monitored to ensure early identification of signs and symptoms of decompensation and/or liver injury. In this study, close and thorough safety monitoring is paired with appropriate investigational product dosing adjustment, interruption, and discontinuation to ensure subject safety.

Investigators, together with the Sponsor's Medical Monitor or designee, will consistently and frequently assess individual subjects, including careful evaluation of signs, symptoms, and laboratory parameters to identify potential hepatic injury and/or decompensation. Criteria for potential hepatic injury and/or progression to decompensation are described in Section 7.4. Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures are described in Section 7.4.4 and Section 7.7.

For subjects randomized to the uptitration arm, special consideration is given to monitoring and management of investigational product as discussed in more detail in Section 9.2. Uptitration criteria have been designed to ensure that only subjects with evidence of adequate functional hepatic reserve will be exposed to the higher OCA dose (25 mg). Specifically, subjects may only be uptitrated at Month 3 if, in addition to no safety or tolerability concerns being identified, they meet strict laboratory criteria (total bilirubin ≤1.2 mg/dL, serum albumin ≥3.5 g/dL, INR <1.5, and platelet count >100,000/mm^3) at both baseline and all visits prior to Month 3. Furthermore, uptitrated subjects must continue to meet those criteria throughout the study to stay on the uptitrated dose; if at any time a subject exceeds these thresholds (including upon retesting), they will be downtitrated to the lower OCA dose (10 mg).

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objectives Assessed at the End of the Double-Blind Phase

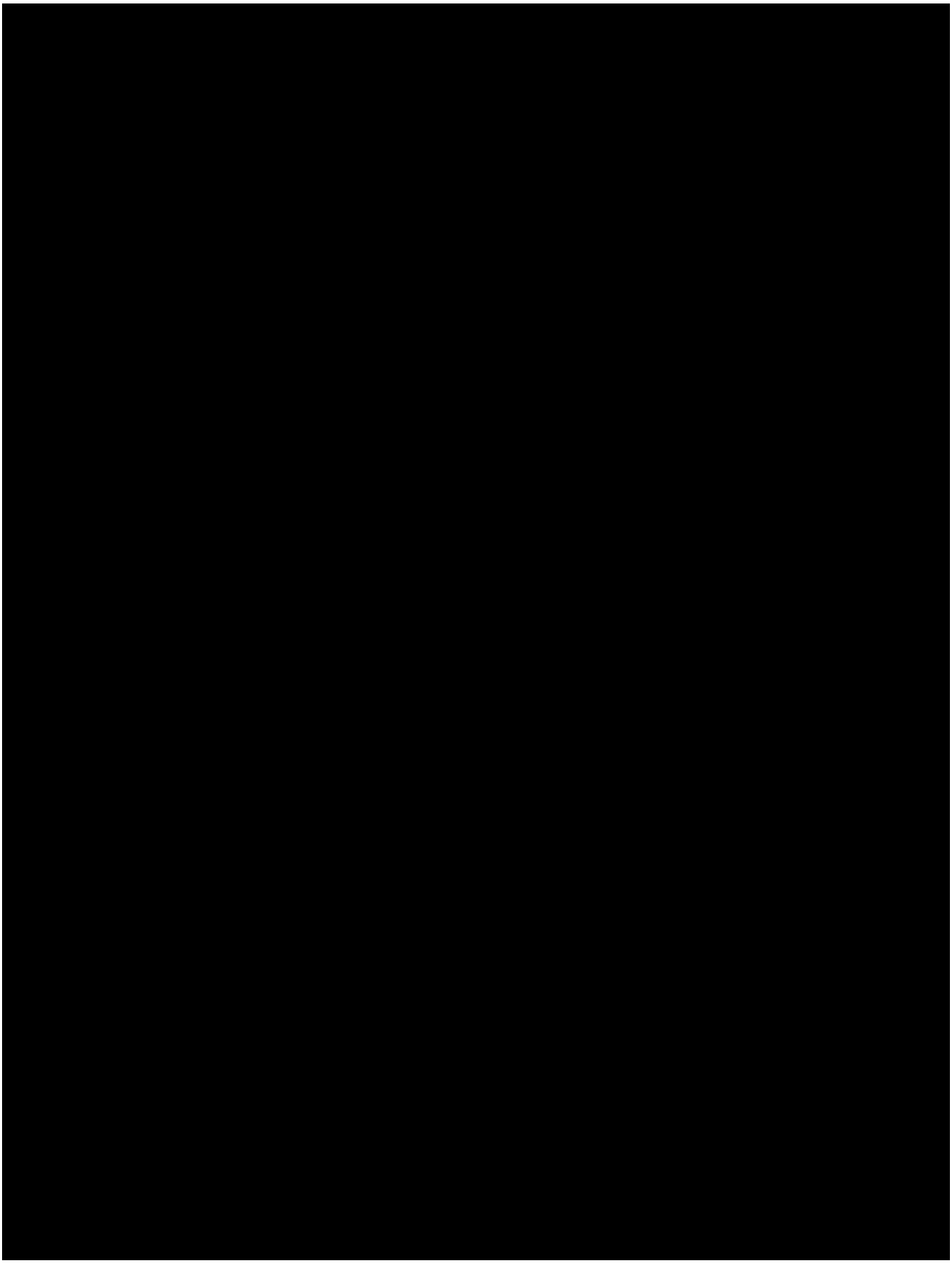
The primary objectives are to evaluate the effects of OCA treatment compared with placebo on:

- Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase

6.2. Secondary Objectives Assessed at the End of the Double-Blind Phase

The secondary objectives are to evaluate the effects of OCA treatment compared with placebo on:

- Resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase
- Resolution of NASH based on pathologist's overall histopathologic interpretation of the presence or absence of definite NASH from Baseline to the end of the Double-Blind Phase
- Histological changes in fibrosis status, including: (1) improvement or (2) no change, from Baseline to the end of the Double-Blind Phase using the NASH CRN scoring system
- Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint):
  - Death (all cause)
  - Liver transplant
  - MELD score ≥15
  - Worsening of CP score (by at least 2 points)
  - Hospitalization (as defined by a stay of ≥24 hours) for:
    - Variceal bleed
    - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
    - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
  - Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)
  - HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy



6.5. Safety Objectives Assessed at the End of the Double-Blind Phase

- To evaluate the safety and tolerability of OCA treatment compared to placebo
- The effect of OCA treatment compared to placebo on the following additional measures and markers:
  - Markers of cardiovascular safety
  - Incidence of adjudicated cardiovascular events
  - Incidence of adjudicated acute kidney injury (AKI) events
  - Incidence of adjudicated events of hepatic injury

6.6. Primary Objectives Assessed at the End of the Open-Label Extension (OLE)

- To evaluate and summarize the longer-term safety and tolerability of OCA treatment
- To summarize the effects of OCA treatment on the occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint):
  - Death (all cause)
  - Liver transplant
  - MELD score ≥15
  - Worsening of CP score (by at least 2 points)
  - Hospitalization (as defined by a stay of ≥24 hours) for:
    - Variceal bleed
    - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
    - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
  - Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)
  - HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 3, double-blind, randomized, placebo-controlled, multicenter international study will evaluate the efficacy and safety of OCA in subjects with a biopsy-confirmed diagnosis of cirrhosis (based on a fibrosis score of 4 using the NASH CRN scoring system) due to NASH (determined by central reading of liver histology). Subjects with hepatic decompensation or CP Class B or Class C cirrhosis are excluded. Subjects who progress to CP Class B or Class C during the study will discontinue investigational product but are expected to be followed through to study closure (or at the discretion of the Sponsor).

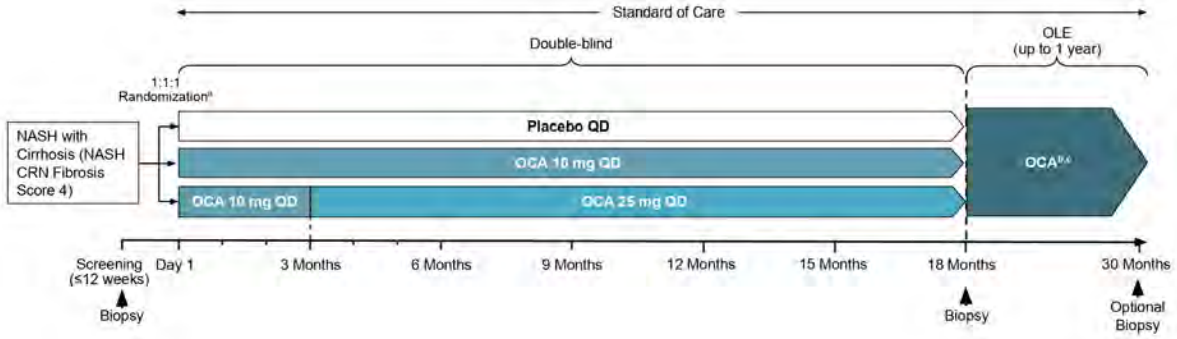
Double-Blind Phase (18 Months): Subjects will be screened for a period of up to 12 weeks before entering the study. Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with local standard of care. Uptitration will be determined based on the laboratory criteria and safety and tolerability assessments completed prior to Month 3 as described in Section 9.2.1.

Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). Investigational product (ie, OCA or placebo) will be taken orally, with water, once daily. Efficacy, safety, and laboratory assessments will be evaluated at clinical visits at Day 1, monthly for the initial 6 months (Month 1 through Month 6 Visits), Month 9, Month 12, Month 15, and Month 18.

Open-Label Extension (up to 12 Months): Subjects who complete the Double-Blind Month 18 Visit and continue to receive investigational product are eligible to enroll into the OLE. All subjects will receive OCA upon entry into the OLE. Subjects randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). Uptitration will be determined based on the same criteria and assessments as employed in the Double-Blind Phase (Section 9.2.1). Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase; however, they will undergo dummy titration to maintain study blind until all subjects complete the Double-Blind Phase and the database is locked (refer to Section 9.2).

7.1.1. Study Design Diagram

Figure 1: Study Design Diagram



CP = Child-Pugh; CRN = clinical research network; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = once daily.

[a] Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with the standard of care

[b] All subjects will receive OCA upon entry into the OLE: Subjects who received placebo during the Double-Blind Phase will be re randomized 1:1 to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at OLE Month 3). Subjects who received OCA during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase.

[c] During the OLE period, subjects will return for site visits at Months 1, 2, 3, 4, 5, 6, 9, and 12.

Note:

- Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH (determined by central reading of liver histology) will be enrolled in the study. Subjects with hepatic decompensation or CP Class B or CP Class C cirrhosis are excluded.
- Two screening visit assessments will be performed. Screening Visit 1 will occur no more than 12 weeks prior to Day 1, and Screening Visit 2 will occur at least 4 weeks after Screening Visit 1.
- Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no).
- The study will remain blinded until all subjects complete the Double-Blind Phase and the database is locked. To maintain blinding, all investigational product (placebo and OCA) tablets and bottles will be identical.

7.1.2. Schedule of Study Procedures

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

	Screening Visit 1[a]	Screening Visit 2[a]	Day 1	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Mth 6	Mth 9	Mth 12	Mth 15	Mth 18/EOT/EOS	ET[b]
Visit Window (Relative to Visit Day)	≤12 Weeks prior to Day 1	≥4 Weeks after SV1	≤12 Weeks after SV1	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	-2 wks	
STUDY PROCEDURES														
Fast ≥8 h Prior to Visit[c]		X	X	X	X	X	X	X	X	X	X	X	X	X
Informed Consent Form	X													
Medical History	X	X	X[d]											
Prior and Concomitant Medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X	X											
Physical Exam	X		X										X	X
Weight, BMI[f]	X		X	X	X	X	X	X	X	X	X	X	X	X
Waist and hip circumference[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[g]	X		X	X	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X		X										X	X
AUDIT, Smoking Habits, and Caffeine Consumption[h]	X[h]		X						X		X		X	X
AEs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Signs and Symptoms of Hepatic Injury or Decompensation			X	X	X	X	X	X	X	X	X	X	X	X
Evaluate Signs and Symptoms of Intercurrent Illness and/or Potential Adverse Events (Appendix C)			X	X	X	X	X	X	X	X	X	X	X	X
HCC Screening (Hepatobiliary Ultrasound[j] and AFP)	X[k]		X[l]						X		X		X	X
Gallbladder Assessment (Ultrasound)	X[k]		X[l]						X		X		X	
EGD Procedure[m]	X													
CP Score/Class (assessment of ascites and HE is required)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

	Screening Visit 1[a]	Screening Visit 2[a]	Day 1	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Mth 6	Mth 9	Mth 12	Mth 15	Mth 18/EOT/EOS	ET[b]
Visit Window (Relative to Visit Day)	**≤12 Weeks prior to Day 1**	**≥4 Weeks after SV1**	**≤12 Weeks after SV1**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**-2 wks**	
MELD Score	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Biopsy[n]		X											X[y]	X
Randomization/Treatment Assigned			X											
Patient-Reported Outcomes and Healthcare Resource Use[o]			X	X		X			X		X		X	X
Pruritus VAS			X	X	X	X	X	X	X	X	X	X	X	X
Dispense/Administer Investigational Product[p]			X	X[q]	X[q]	X	X[q]	X[q]	X	X	X	X		
Assess Investigational Product Accountability & Compliance				X	X	X	X	X	X	X	X	X	X	X
CLINICAL AND LABORATORY EVALUATIONS														
Serum Chemistry[r], Hematology, Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Free Fatty Acids			X						X		X		X	X
Review Potential DILI Management Algorithm (Liver Biochemistry)				X	X	X	X	X	X	X	X	X	X	X
Glucose and HbA1c	X		X	X[s]	X[s]	X	X[s]	X[s]	X	X	X	X	X	X
Insulin, C-Peptide, HOMA-β, and HOMA-IR			X	X					X		X		X	X
Lipoprotein Analysis			X						X				X	X
Thyroid Hormones			X						X				X	X
Virology (HCV, HBsAg)	X													
Urinalysis	X		X										X	X
Urine-Based β-hCG Pregnancy Test[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NFS, FIB-4, and APRI	X		X	X	X	X	X	X	X	X	X	X	X	X

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

	Screening Visit 1[a]	Screening Visit 2[a]	Day 1	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Mth 6	Mth 9	Mth 12	Mth 15	Mth 18/EOT/EOS	ET[b]
Visit Window (Relative to Visit Day)	**≤12 Weeks prior to Day 1**	**≥4 Weeks after SV1**	**≤12 Weeks after SV1**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**-2 wks**	
TE and MRE (conducted at sites where device is available)[u]	X	X	X						X				X	X
ELF and FibroMeter			X			X			X		X		X	X
Markers of Inflammation, Apoptosis, and Necrosis			X	X		X	X		X		X		X	X
[redacted]			[redacted]						[redacted]				[redacted]	[redacted]
Cardiovascular Risk Scores (10-year ASCVD Risk, FRS, Reynolds Score, SCORE)			X								X		X	X
Trough PK Blood Samples[v] (All Subjects)				X		X	X		X		X		X	X
PD Blood Samples (All Subjects)			X	X		X	X		X		X		X	X
[redacted]			[redacted]			[redacted]			[redacted]				[redacted]	
OPTIONAL ASSESSMENTS														
Serial PK Blood Samples[x]				X			X				X		X	

AE = adverse event; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; APRI = aspartate aminotransferase to platelet ratio index; AST = aspartate aminotransferase; ASCVD = atherosclerotic cardiovascular disease; AUDIT = Alcohol Use Disorders Identification Test; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; CLDQ-NAFLD = chronic liver disease Questionnaire-Nonalcoholic Fatty Liver Disease; CP = Child-Pugh; eCRF = electronic case report form; DILI = drug-induced liver injury; EDC = electronic data capture; EGD = esophagogastroduodenoscopy; ELF = Enhanced Liver Fibrosis; EOS = End of Study; EOT = End of Treatment; EQ-5D-5L = EuroQol five dimensions questionnaire; ET = early termination; FIB-4 = Fibrosis-4; FRS = Framingham Risk Score; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HE = hepatic encephalopathy; HOMA-β = homeostatic model assessment-beta cell; HOMA-IR = homeostatic model assessment-insulin resistance; ICF = informed consent form; MELD = model for end-stage liver disease; MRE = magnetic resonance elastography; Mth = month; NAFLD = nonalcoholic fatty liver disease; NFS = NAFLD fibrosis score; PD = pharmacodynamics; PK = pharmacokinetics; SCORE = systemic coronary risk evaluation; SV = screening visit; TE = transient elastography; VAS = visual analog scale; wk = week; WPAI = Work Productivity and Activity Index

[a] Screening Visit 2 must occur at least 4 weeks after Screening Visit 1 to confirm pretreatment serum chemistry levels, including ALT, AST, and total bilirubin. Biopsy, EGD, ultrasound, TE, and MRE do not have to be performed on the same day as Screening Visit 1 or Screening Visit 2.

[b] For ET, as soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Instruct the subject to fast overnight (at least 8 hours) before each visit. Fasting is required before all study visits, but water is permitted.

[d] Assessment of baseline pruritus only.

[e] Prior medications taken within 12 months of Day 1 are to be recorded at Screening Visits 1 and 2, and Day 1 only. For all other visits, only concomitant medications are to be recorded.

[f] Height will be measured at Screening Visit 1 only. The calculations for BMI and waist-to-hip ratio will be performed via EDC: BMI from weight and height measurements, and waist-to-hip ratio from waist and hip circumference measurements.
[g] Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes.
[h] At Screening Visit 1, only AUDIT will be conducted. At D1, M6, M12, M18/EOT/EOS, and ET, all 3 assessments (AUDIT, smoking habit, and caffeine consumption) will be done.
[i] AEs occurring after signing of the ICF must be entered on the AE eCRF.
[j] For subjects who develop HCC during the study, HCC screening assessments for study visits after onset of HCC are not required.
[k] Hepatobiliary ultrasound for HCC screening and gallbladder assessments at Screening are not required if data from a recent historic ultrasound (within 3 calendar months of Day 1) are available.
[l] Ultrasound will be conducted to enhance HCC surveillance and for gallbladder assessment. If ultrasound was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound.
[m] Perform EGD procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with endoscopic evidence of varices will not be enrolled in the study.
[n] On-study liver biopsies should be performed after the hepatobiliary ultrasound for HCC screening. Liver biopsy procedure is not required for subjects who have had a biopsy ≤12 months prior to randomization (Day 1) and can provide unstained slides for central reading. Liver biopsy at ET is an optional procedure.
[o] Health-related quality of life [redacted] and standardized generic measure of health status for the assessment of health utilities (eg, hospitalization [reason, length of stay, major medical procedures], emergency room visits, outpatient physician visits, concomitant medications).
[p] All assessments, except for the post-dose collection of blood samples for the subjects participating in the PK and/or [redacted], must be completed prior to administration of investigational product.
[q] At the Months 1, 2, 4, and 5 visits, investigational product administered will be from the bottle dispensed at a previous visit.
[r] In the event the Screening Visit 2 value for ALT, AST, or total bilirubin (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome) is ≥30% higher than the Screening Visit 1 value and > ULN, then a third measurement must be obtained at an unscheduled visit.
[s] Glucose only
[t] Urine β-hCG pregnancy tests must be performed for females of childbearing potential before entry. If positive, a confirmatory blood test must be performed. If the blood test is also positive, the subject may not be enrolled in the study, and if already enrolled, must be discontinued immediately.
[u] TE by Fibroscan® and MRE will be conducted at sites where device is available. Baseline TE should be performed once at Screening Visit 1, Screening Visit 2, or Day 1 (prior to first study drug administration). It is encouraged that TE is conducted prior to on-study liver biopsy(-ies). MRE will be conducted only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects.
[v] Trough PK samples will be collected from all subjects at each specified visit and must be completed prior to administration (predose) of investigational product.
[w] [redacted]
[x] Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose of investigational product. All assessments, except for the post-dose collection of blood samples for subjects participating in the PK assessment, must be completed prior to administration of investigational product. Subjects will be permitted to decline to participate without affecting their involvement in the study.
[y] When a subject completes a liver biopsy as part of the EOT visit during the Double-Blind Phase, and remains in the study, a second biopsy is not required at the Month 18 Visit.

Table 2: Schedule of Study Procedures (OLE Phase)

Note: Only those subjects who complete the Double-Blind Month 18 Visit and continue to receive investigational product are eligible to enroll into the OLE. OLE visit dates are based off of the OLE Day 1 first dose

	OLE Day 1[a] (Month 18 DB)	OLE M1	OLE M2	OLE M3	OLE M4	OLE M5	OLE M6	OLE M9	OLE M12/ EOT/EOS	ET[b]
Visit Window (Relative to Visit Day)	-2 wks	±1 wk	±1 wk	±1wk	±1 wk	±1 wk	±1 wk	±1 wk	-2 wk	
STUDY PROCEDURES										
Fast ≥8 h Prior to Visit[c]	X	X	X	X	X	X	X	X	X	X
Informed Consent[d]	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physical Exam	X								X	X
Weight, BMI[e]	X	X	X	X	X	X	X	X	X	X
Waist and Hip Circumference[e]	X	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X								X	X
AUDIT, Smoking Habits, and Caffeine Consumption	X						X		X	X
AEs	X	X	X	X	X	X	X	X	X	X
Assess Signs and Symptoms of Hepatic Injury or Decompensation	X	X	X	X	X	X	X	X	X	X
Evaluate Signs and Symptoms of Intercurrent Illness and/or Potential Adverse Events (Appendix C)	X	X	X	X	X	X	X	X	X	X
HCC Screening (Hepatobiliary Ultrasound[g] and AFP)	X						X		X	X
EGD Procedure[h]	X									
CP Score/Class (assessment of ascites and HE is required)	X	X	X	X	X	X	X	X	X	X
MELD Score	X	X	X	X	X	X	X	X	X	X
Randomization/Treatment Assigned[i]	X									
Liver Biopsy	X[i]								X[j]	X[j]
Dispense/Administer Investigational Product[k]	X	X[l]	X[l]	X	X[l]	X[l]	X	X		

Table 2: Schedule of Study Procedures (OLE Phase) (Continued)

	OLE Day 1[a] (Month 18 DB)	OLE M1	OLE M2	OLE M3	OLE M4	OLE M5	OLE M6	OLE M9	OLE M12/ EOT/EOS	ET[b]
Visit Window (Relative to Visit Day)	**-2 wks**	**±1 wk**	**±1 wk**	**±1wk**	**±1 wk**	**±1 wk**	**±1 wk**	**±1 wk**	**-2 wk**	
Assess Investigational Product Accountability & Compliance	X	X	X	X	X	X	X	X	X	X
CLINICAL AND LABORATORY EVALUATIONS										
Serum Chemistry, Hematology, Coagulation	X	X	X	X	X	X	X	X	X	X
Free Fatty Acids	X						X		X	X
Review Potential DILI Management Algorithm (Liver Biochemistry)	X	X	X	X	X	X	X	X	X	X
Glucose and HbA1c	X	X[l]	X[l]	X	X[l]	X[l]	X	X	X	X
Insulin, C-Peptide, HOMA-β, and HOMA-IR	X	X					X		X	X
Lipoprotein Analysis	X		X			X	X		X	
Thyroid hormones	X						X		X	X
Urinalysis	X						X		X	X
Urine-Based β-hCG Pregnancy Test[n]	X	X	X	X	X	X	X	X	X	X
Cardiovascular Risk Scores (10-year ASCVD Risk, FRS, Reynolds Score, SCORE)	X								X	X
NFS, FIB-4, and APRI	X	X	X	X	X	X	X	X	X	X
TE (conducted at sites where device is available)	X[o]						X		X	
ELF and Fibrometer	X			X			X		X	

AE = adverse event; AFP = alpha-fetoprotein; APRI = aspartate aminotransferase to platelet ratio index; ASCVD = atherosclerotic cardiovascular disease; AUDIT = Alcohol Use Disorders Identification Test; β-hCG = beta human chorionic gonadotropin; BMI = body mass index; CP = Child-Pugh; DB = double-blind; DILI = drug-induced liver injury; EDC = electronic data capture; EGD = esophagogastroduodenoscopy; ELF = Enhanced Liver Fibrosis; EOT = end of treatment; EOS = end of study; ET = early termination; FIB-4 = Fibrosis-4; FRS = Framingham Risk Score; HbA1c = hemoglobin A1c; HCC = hepatocellular carcinoma; HE = hepatic encephalopathy; HOMA-β = homeostatic model assessment-beta cell; HOMA-IR = homeostatic model assessment-insulin resistance; ICF = informed consent form; MELD = model for end-stage liver disease; NAFLD = nonalcoholic fatty liver disease; NFS = NAFLD fibrosis score; OCA = obeticholic acid; OLE = open-label extension; SCORE = systemic coronary risk evaluation; TE = transient elastography; wk = week

[a] If the procedure indicated was performed at the end of the Double-Blind Phase, it is not necessary to repeat, unless the Investigator determines otherwise. The day of the first dose from the OLE bottle is considered OLE Day 1. OLE visit windows are based on the OLE Day 1 first dose

[b] For ET, as soon as possible upon study discontinuation and as near as possible to last dose taken.

[c] Instruct the subject to fast overnight (for at least 8 hours) before each visit. Fasting is required before all study visits, but water is permitted.

[d] The OLE ICF may be obtained as early as Month 15 of the Double-Blind Phase.

[e] The calculations for BMI and waist-to-hip ratio will be performed via EDC: BMI from weight and height measurements, and waist-to-hip ratio from waist and hip circumference measurements. (Note: Height will be measured at Screening Visit 1 only.)
[f] Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes.
[g] For subjects who develop HCC during the study, HCC screening assessments for study visits after onset of HCC are not required.
[h] Perform EGD procedure unless data from a recent EGD (within 6 months of OLE Day 1) are available. Subjects with endoscopic evidence of varices will not continue in the OLE Phase.
[i] Subjects randomized to placebo during the Double-Blind Phase will be re-randomized to OCA 10 mg or OCA 10 mg → 25 mg arms on OLE Day 1; the placebo subjects in the OCA 10 mg → 25 mg arm will receive OCA 10 mg for 3 months followed by OCA 25 mg in the OLE if the uptitration criteria are met (Section 9.2). Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the treatment they were assigned.
[j] Biopsy at Month 18 DB/Day 1 OLE, must be completed prior to receiving investigational product on Day 1 of OLE. At Month 12 of OLE and ET of OLE, the biopsy procedure is optional.
[k] All assessments must be completed prior to administration of investigational product. The first dose of OLE investigational product should be taken the day after the Month 18 assessments are completed.
[l] At the OLE Month 1, 2, 4, and 5 Visits, investigational product dispensed/administered will be from the bottle issued at the previous visit.
[m] Glucose only
[n] Urine β-hCG pregnancy tests must be performed for females of childbearing potential. If positive, a confirmatory blood test must be performed. If the blood test is also positive, the subject may not be continued in the study.
[o] MRE will be conducted as part of the Month 18 DB EOT Visit.

7.1.3. Study Duration

The maximum duration of individual subject participation for this study is approximately 2 years and 9 months, including a Screening Period of up to 12 weeks, an 18-month Double-Blind Phase, and an OLE Phase expected to last approximately 1 year.

7.2. Number of Subjects

Approximately 900 subjects will be enrolled in the study.

7.3. Planned Dosing Regimen

Subjects will be randomly assigned in a 1:1:1 ratio to receive OCA 10 mg, OCA 10 mg → 25 mg, or placebo.

For subjects in the OCA 10 mg → 25 mg group, a dose titration to 25 mg will be implemented at Month 3 after assessments of liver chemistry and safety at Month 1 and Month 2, unless there are safety and tolerability concerns identified by the Medical Monitor/or the Investigator. Subjects randomized to the OCA 10 mg or placebo arms will continue the same dosing (dummy titration) (refer to Section 9.2).

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

To monitor for potential hepatic injury, disease progression and/or hepatic decompensation, CP and MELD scores will be reviewed at each visit (Section 7.1.2). In addition, adverse events, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in the following subsections (Section 7.4.1 to Section 7.4.3). Based on the assessments of signs and symptoms of hepatic injury and liver biochemistry, the investigational product will be interrupted or discontinued per criteria discussed in Section 7.7, and close monitoring procedures will be implemented (refer to Section 7.4.4).

7.4.1. Signs and Symptoms of Hepatic Injury or Decompensation

The Investigator will educate each subject about recognizing the signs and symptoms of potential hepatic injury or decompensation and instruct each subject to contact the study site to report the onset of any new or worsening signs and symptoms during the study. The Investigator will instruct subjects to seek immediate medical attention if they experience signs or symptoms of hepatic injury or decompensation.

Appendix C provides guidance for review of signs and symptoms of hepatic injury or decompensation described below to be evaluated at each study visit, or as frequently as needed per Investigator's discretion.

Subjects will be evaluated at study visits for potential signs and symptoms of hepatic injury or decompensation:

Signs and Symptoms of Hepatic Injury or Decompensation:

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

Other Symptoms:

- New or worsening pruritus
- Decreased urine output, urine color change, dizziness, lethargy

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 potential drug-induced liver injury (DILI) (Section 7.4.2), (2) assessment for disease progression (Section 7.4.3), (3) triggering of investigational product interruption or discontinuation per criteria (Section 7.7), (4) documentation in the AE eCRF or the SAE eCRFs (Section 16.1), and (5) contact with the medical monitor.

7.4.2. Potential Drug-Induced Liver Injury

Events of potential hepatic injury will be reviewed and adjudicated by the Hepatic Safety Adjudication Committee (HSAC) as described in Section 17.14. The specific criteria for identification and adjudication of potential hepatic injury events are described in the HSAC charter.

Liver biochemistries will be assessed at each visit to assess biochemical triggers that will prompt an immediate reevaluation of subjects. Thus, these assessments will be performed at:

- Each protocol-specified visit
- Unscheduled visits for any safety follow-up as appropriate

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 laboratory is required. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges. Of note, the Baseline result is the average of results from Screening Visits 1 and 2, Day 1, and any unscheduled visit that took place between Screening Visit 1 and the Day 1 Visit. All local laboratory data, including the reference ranges, are to be collected and entered in the eCRF within 2 days of receiving the results. For guidance on alternative processes under which subjects may complete the protocol-specified assessments under COVID-19 restrictions refer to Section 10. Local laboratory visits in conjunction with remote (telemedicine) visits are specifically encouraged in lieu of on-site visits where subject's safety is of concern (eg, adverse event monitoring).

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and potentially a complete subject evaluation (depending on the repeat result) are summarized in Table 3.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; BL = baseline; eCRF = Electronic Case Report Form; INR = international normalized ratio; IP = Investigational Product; PK = pharmacokinetic; TB = total bilirubin; ULN = upper limit of normal.

Laboratory assessments include: [redacted]

[a] Signs and symptoms of hepatic injury include severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, and eosinophilia. Decompensation events include variceal hemorrhage, hepatic encephalopathy, and ascites

[b] Lower severity treatment-emergent threshold criteria include the following from Table 3: In subjects with baseline ALP ≤ULN and treatment-emergent ALP ≥2x BL and >ULN but <250 U/L

[c] If a subject is unable to return to the site for repeat test, the subject MUST have repeat (or any safety) laboratory tests performed at a local laboratory. All local laboratory results, including reference ranges, should be entered in the eCRF within 2 days of receiving results.

[d] PK sampling must be conducted within 7 days of IP interruption; close monitoring including physical exams and repeat laboratory testing should occur as often as deemed appropriate by the Investigator. In subjects with signs or symptoms of hepatic injury or events of hepatic decompensation, the Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject.

[redacted]

If any subject meets the triggering threshold limits indicated in Table 3 and experiences signs or symptoms of hepatic injury (severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, eosinophilia) or events of decompensation (varices hemorrhage, hepatic encephalopathy, or ascites), which can be presenting features of DILI in subjects with cirrhosis, investigational product should be immediately interrupted (see Section 7.7 for dosing modifications).

If no signs or symptoms of hepatic injury or decompensation are present, but liver biochemistries are above the triggering threshold limits, the subject should either interrupt investigational product or laboratory assessments including creatine phosphokinase (CPK) should be repeated within 2-4 days according to the threshold limits specified in Table 3. If a repeat laboratory test cannot be performed within 7 days of receiving results, the subject should be instructed to interrupt investigational product until repeat laboratory test results have been reviewed.

If investigational product is interrupted, laboratory assessments including CPK should be repeated within 2-4 days of receiving results, a PK sample must be collected (within 7 days), and close monitoring should be initiated (repeat laboratory testing and physical exam should occur as often as deemed appropriate by the Investigator and these data should be entered in the eCRF within 2 days of receiving results). In subjects with signs or symptoms of hepatic injury or events of decompensation, the Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject.

- If on repeat evaluation, in subjects who did not have investigational product interrupted (eg, those that had no signs and symptoms and lower severity), liver biochemistries are normal or below threshold values, no dosing modifications are required and the subject should continue to be monitored closely.
- If on repeat evaluation, liver biochemistries remain elevated (see Table 3), investigational product must be interrupted for a minimum of 30 days, a PK sample (see below for OCA and metabolites) must be collected (within 7 days of receiving results), and close monitoring should be initiated (repeat laboratory testing and physical exam should occur as often as deemed appropriate by the Investigator and these data should be entered in the eCRF within 2 days of receiving results). The medical monitor should be promptly contacted upon awareness for consultation regarding management of the subject.

In any subject for whom investigational product is interrupted for reasons other than the inability to promptly repeat laboratory testing (within 7 days) for non-safety reasons, a rechallenge may be considered after a minimum of 30 days if liver enzymes return to below threshold values, there are no symptoms, lab abnormalities are determined not to be due to DILI, and if approved by the Medical Monitor and Investigator. If investigational product is restarted after 30 days, liver biochemistries should be repeated within 2 to 4 days and close monitoring should be continued.

If the liver enzymes do not return to below threshold values after 30 days and the Investigator considers that the event has not resolved, the Investigator should consult with the Medical Monitor to determine a treatment plan. This may include continuing close monitoring with interruption or discontinuing investigational product.

For all subjects whose investigational product is interrupted or discontinued, and close monitoring is initiated, a follow up assessment of the subject's status should be performed at study completion.

Subjects should, wherever possible, come back to the site. It may be difficult for subjects who are distant from their study site to return to the site promptly. Such subjects must have repeat (or any safety) laboratory tests performed at a local laboratory, but normal laboratory ranges and the results should be made available to the Investigator All local laboratory data, including reference ranges, should be entered in the eCRF within 2 days of receiving the results. For guidance on alternative processes under which subjects may complete the protocol-specified assessments under COVID-19 restrictions refer to Section 10.

It should be noted that it is difficult to recognize every potential marker of hepatic deterioration. 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 artefactual; 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.

Specific aspects of the Potential DILI Management Algorithm may be adjusted, in which case specific guidelines will be provided to the sites for implementation.

7.4.3. Progression of Disease to Child-Pugh Class B or C

Investigators will closely monitor subjects for potential progression of cirrhosis to CP Class B or Class C at every visit (or at unscheduled visits in the event of signs or symptoms of potential hepatic injury or decompensation). Assessment of CP Scores must be performed at every visit. Refer to Section 7.4.3.1 for determination of CP Score. Investigational product discontinuation is required in subjects who progress to CP score of 7 or higher.

7.4.3.1. Child-Pugh Assessment

CP Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 4 and can range from 5 to 15. The investigational product should be discontinued in subjects with CP score ≥7.

Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which should be collected at the same visit. The relationship of CP Score to disease progression is as follows: CP score 5-6 = CP Class A; CP Score 7-9 = CP Class B; CP Score ≥10 = CP Class C.

Table 4: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum total 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]		None	Grade 1 or 2	Grade 3 or 4

INR = international normalized ratio
Child-Pugh criteria: Pugh 1973, Lucey 1997.
West Haven criteria: Vilstrup 2014.
[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

7.4.3.2. Model for End-Stage Liver Disease (MELD) Scoring

MELD is a scoring system used to assess the severity of chronic liver disease. An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. MELD scores will be calculated based on creatinine, bilirubin, INR, and serum sodium values as appropriate, collected at the same visit with modification by United Network for Organ Sharing. If only 1 component of MELD needs to be repeated, all other components should also be repeated. INR will be calculated based on PT value by the central laboratory. The MELD calculation adjusts for subject who have had 2 or more dialysis treatments within the prior week and will automatically assign a serum creatinine of 4.0 mg/dL for these subjects.

7.4.4. Close Observation

The Investigator should consistently and frequently assess individual subjects who meet the above criteria to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury or decompensation coupled with rules-based laboratory monitoring. If investigational product is interrupted or discontinued as described in Section 7.7, subjects should continue to be closely monitored based on the clinical judgement of the Investigator and evaluated for signs and symptoms of potential hepatic injury. In the event of potential hepatic injury, the subject should be promptly brought into the clinic and undergo a complete evaluation (laboratory assessments, physical examinations, and review of signs and symptoms). Subjects who permanently discontinue from investigational product are not required to undergo additional safety visits provided stabilization

of the clinical event leading to discontinuation has occurred (per discretion of the Investigator and upon discussion with the Medical Monitor).

At a minimum, the following assessments should be conducted at each study visit:

- Exam and thorough review of subject reported signs and symptoms of hepatic injury or decompensation (see Appendix C),
- [redacted] and MELD scores.

In addition, a PK sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any subject who develops an AE of hepatic injury or decompensation or interrupts investigational product due to potential hepatic injury (Section 7.4.2).

For events of potential hepatic injury, the following additional monitoring procedures should be performed per FDA Guidance for Industry on Drug Induced Liver Injury. These cases need to be discussed with the Sponsor's Medical Monitor:

- Repeating liver enzyme and serum bilirubin tests as described in Table 3. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic, as clinically indicated.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs that are potentially hepatotoxic, continued use of investigational product should be discussed with the Sponsor's Medical Monitor. The subject may be discontinued from investigational product, if clinically appropriate.
- Obtaining a history of exposure to environmental chemical agents or herbal supplements that may be associated with liver toxicity.
- Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute HBV infection), and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).
- Seeking hepatology consultation, if the Investigator is not a hepatologist.

For all subjects whose investigational product is interrupted or discontinued, and close monitoring is initiated, a follow up assessment of the subject's status should be performed at study completion.

7.4.5. Pruritus

Pruritus is already being closely monitored but has not been shown to be a reliable predictor of hepatic injury. However, Investigators should be vigilant in responding to subjects' complaints of new or worsening pruritus symptoms with prompt follow-up. Pruritus grading (as with all adverse events) should be performed in accordance with the current version of the Common Terminology Criteria for Adverse Events (CTCAE;Appendix D).

For subjects with Grade 3 pruritus per the current version of the CTCAE (Section 16.1.6.1), instruct the subject to discontinue investigational product (Table 5). These subjects should continue to return for scheduled study visits for safety follow up; however, the subjects will not be rechallenged with investigational product. General guidance for the management of subjects experiencing significant pruritus (≤ Grade 2) is provided in Section 16.1.6.1.

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

7.5.1. Symptomatic Cholelithiasis and/or Cholecystitis

NASH is associated with several known risk factors for cholelithiasis, such as obesity, type 2 diabetes, and other metabolic abnormalities. The prevalence of gallstone disease in NASH is higher than in the general population. The majority of gallstones are asymptomatic and may never become symptomatic (Sakorafas 2007, Stinton 2012).

Because symptomatic events of cholelithiasis and/or cholecystitis may develop in subjects with or without a known history of gallstones, it is important that all subjects be (1) monitored for signs and symptoms suggestive of gallstone disease and (2) counseled to recognize and seek immediate medical attention if they experience symptoms suggestive of cholelithiasis and/or cholecystitis.

Subjects who develop signs or symptoms suggestive of symptomatic cholelithiasis (refer to Appendix C) and/or complications related to gallstone disease (eg, cholecystitis) should have investigational product interrupted while undergoing further evaluation consistent with the local standard of care and management until complete resolution, including potential surgical intervention.

Post-cholecystectomy, subjects should be monitored for full resolution and may resume investigational product after approval from the Investigator and Medical Monitor (see Section 7.7).

If upon surgical evaluation, it is deemed that the subject does not need to undergo surgery, the subject may re-initiate investigational product upon resolution of symptoms and approval from the Investigator and Medical Monitor.

7.5.2. Pancreatitis

Pancreatitis is a serious and potentially fatal condition most commonly caused by gallstones or alcohol.

Because symptoms of acute pancreatitis and acute cholecystitis may be similar, subjects presenting with significant upper abdominal pain with nausea, vomiting, fever, or jaundice

should be evaluated for both cholecystitis and pancreatitis, consistent with the local standard of care (eg, amylase and lipase laboratory tests and/or imaging assessments).

Investigational product must be permanently discontinued in any subject diagnosed with treatment-emergent acute, or nonacute (chronic or recurrent) pancreatitis (see Section 7.7). The evidence used to diagnose pancreatitis, including symptoms, laboratory test results, and/or imaging results, must be collected. 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 local standard of care. The Investigator should contact the Medical Monitor upon awareness of treatment-emergent acute or nonacute pancreatitis.

Investigational product discontinuation is not required for subjects who have a medical history of pancreatitis and have not experienced recurrence of pancreatitis since enrollment into the study. Any subject who meets the requirements for investigational product discontinuation should be encouraged to remain in the study and complete all protocol-specific assessments as defined, after stopping investigational product.

7.6. Monitoring for Renal Impairment and Nephrolithiasis

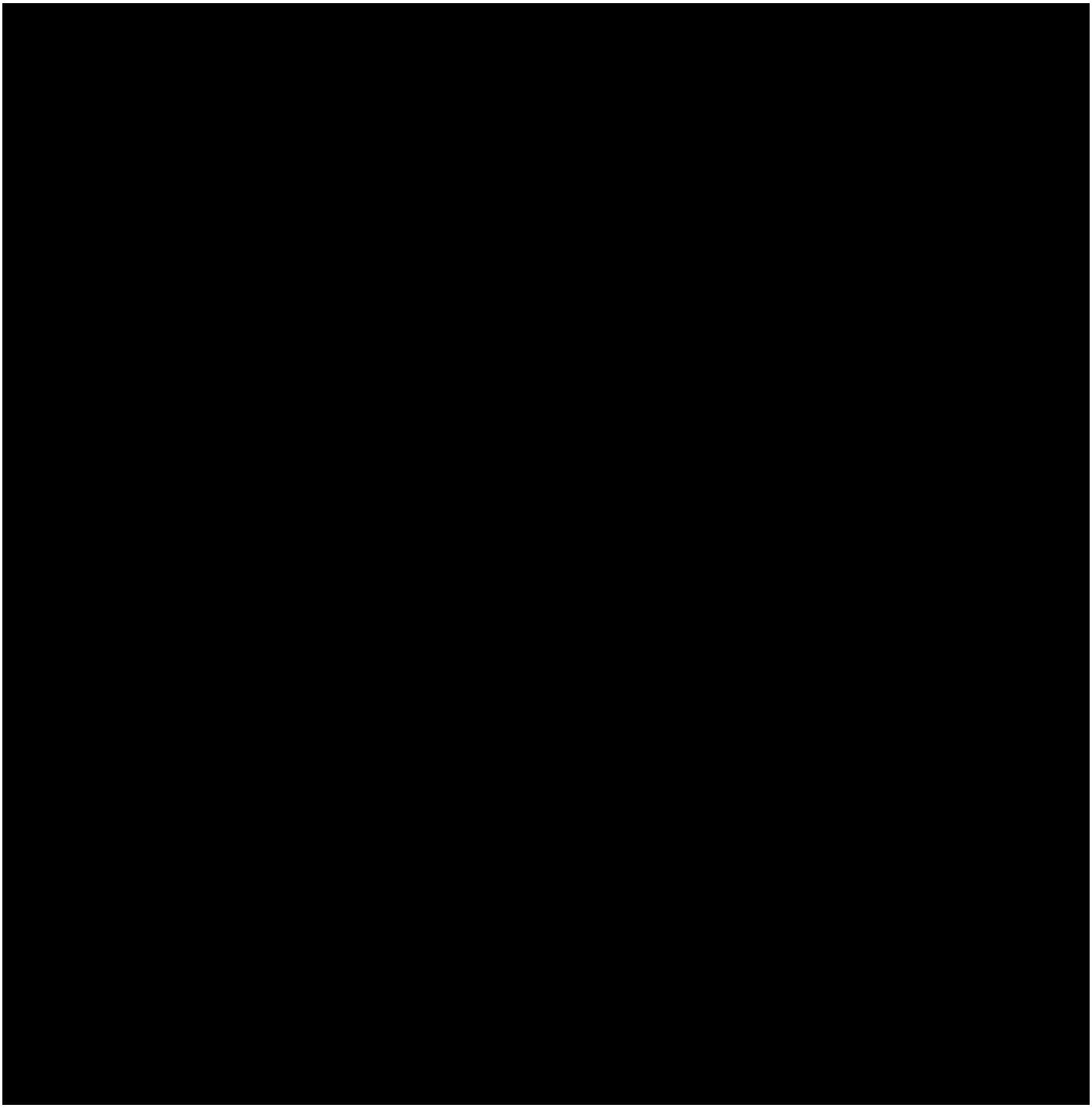
7.6.1. Renal Impairment

AKI is a serious medical condition that may lead to chronic kidney disease or kidney failure; therefore, it is important to identify and monitor subjects for signs or symptoms suggestive of AKI for appropriate management. Investigators are instructed to evaluate for symptoms suggestive of AKI such as new onset fatigue/asthenia, nausea, or confusion and to assess signs such as decreased skin turgor (dehydration), increased heart rate, lower extremity edema, decrease urine output or dark urine at each visit.

As AKI is defined by an abrupt decrease in renal function, the Sponsor recognizes that local labs will be required to be recorded as well as all central lab data (scheduled or unscheduled visits) to adequately capture events. Repeat laboratory assessments should include albumin, serum chemistry (creatinine, BUN, electrolytes), urinalysis with microscopic examination, and assessment of eGFR. All local lab data, including reference ranges, are required to be entered in the eCRF within 2 days of receiving results.

The threshold criteria used to identify and monitor subjects for potential renal impairment and the actions to be taken with investigational product are outlined in Figure 3.

Baseline serum creatinine values, which will inform the subsequent decisions on monitoring for and management of renal injury, are defined as the average of serum creatinine values from the two most recent study visits (scheduled and unscheduled), that are not associated with a renal-related AE or an acute increase.



If a subject meets the threshold criteria, a prompt re-evaluation (within 48 hours) should take place. Subjects should, when possible, return to the study site for re-evaluation. It may be difficult for subjects who are distant from their study site to return to the site promptly. Such subjects must have repeat (or any safety) laboratory tests performed at a local laboratory, but the laboratory reference ranges and the results should be made available to the Investigator. All local laboratory data, including reference ranges, should be entered into the eCRF within 2 days of receiving the results.

- If on repeat testing, serum creatinine has returned to below threshold values, no dosing modifications are required.
- If on repeat testing, serum creatinine remains elevated a comprehensive evaluation including the subject's recent medical history, changes in medication, health status, and intercurrent illness should be conducted. If no alternative cause of serum creatinine elevation can be identified investigational product should be interrupted and close monitoring should be initiated. Close monitoring includes repeat labs and physical exam, which should occur as often as deemed appropriate by the Investigator, and these data should be entered in to the eCRF within 2 days of receiving results. If deemed appropriate by the Investigator, the subject may be referred to a nephrologist.

In any subject for whom investigational product is interrupted for reasons other than inability to promptly repeat laboratory assessments for non-safety reasons:

- The event will be treated as a potential case of AKI and will be sent for review and adjudication by the Renal Adjudication Committee (described in Section 17.11.2). The specific criteria for identification and adjudication of potential AKI events are described in the Renal Adjudication Committee charter.
- A PK sample must be collected within 7 days of investigational product interruption. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.
- A rechallenge may be considered after a minimum of 30 days if serum creatinine returns to below threshold values and if approved by the Medical Monitor and Investigator. If serum creatinine remains above threshold values after 30 days, the subject should be referred to a nephrologist for further evaluation.

7.6.2. Nephrolithiasis

The development of signs or symptoms suggestive of kidney stones (nephrolithiasis) should be monitored. Standard of care including adherence to recommended dietary measures, adequate fluid intake, and other measures prescribed should be employed to prevent recurrent episodes of kidney stones (Pearle 2014). Subjects should be asked if they have experienced symptoms of nephrolithiasis (eg, evidence of hematuria or flank pain). Nephrolithiasis should be considered in subjects with evidence of microscopic hematuria without other symptoms.

Subjects who develop kidney stones during the study will be further evaluated according to guidelines to collect serum electrolytes, uric acid, and a urinalysis with microscopic examination (Pearle 2014). All local laboratory data, including reference ranges, should be entered into the eCRF within 2 days of receiving the results. Every effort should be made to collect the kidney stone for analysis. Subjects should be referred to a urologist or nephrologist for further evaluation of the nephrolithiasis, including the etiology as appropriate.

7.7. Investigational Product Dosage Interruption, Downtitration, Discontinuation, and Rechallenge Criteria

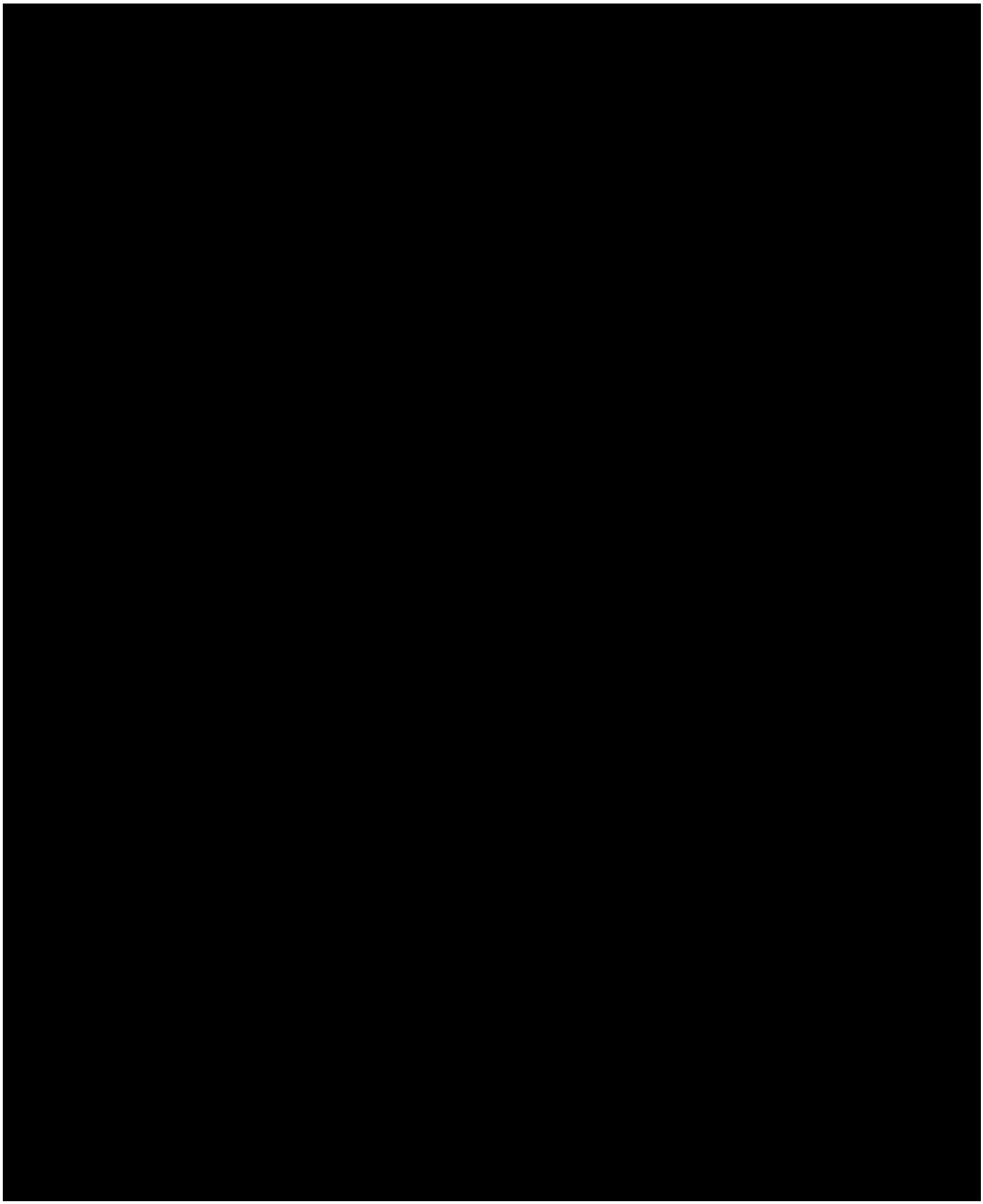
Dosages for investigational product should be maintained constant during the study. However, interruptions, downtitration, discontinuation, and any rechallenge of investigational product should be implemented per the criteria outlined in Table 5. Planned uptitration at Month 3 in the OCA 10 mg → 25 mg arm (Double-Blind Phase) and in placebo subjects at OLE Month 3 is described in Section 9.2.

Subjects can be temporarily or permanently discontinued from investigational product by the Investigator at any time for clinical safety concerns. If investigational product is temporarily or permanently discontinued, a PK sample must be collected within 7 days. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.

- Subjects who are temporarily discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study.
- Subjects who permanently discontinue from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. These subjects will not be rechallenged with investigational product.

Prior to re-starting investigational product after a prolonged interruption, the subject must be re-consented and new baseline visit procedures must be performed (refer to Section 8.2.2) if the interval from the last visit was more than 3 months (+2 weeks).

Investigational product should **not** be interrupted in the following instances: 1) in subjects who experience an event that is not symptomatic (such as an incidental finding of gallstones during an ultrasound exam); 2) in subjects who previously experienced an event of symptomatic cholelithiasis and/or cholecystitis and have either undergone a cholecystectomy (and have no symptoms suggestive of retained or recurrent bile duct stones) or upon surgical consultation does not need to undergo surgery, and in whom symptoms have fully resolved at the present time while on investigational product; or 3) in subjects who have a past medical history of pancreatitis and have not experienced a recurrence of pancreatitis since enrollment into the study.



7.8. Criteria for Study Termination

The Sponsor reserves the right to terminate the study at any time. It is normal procedure to review the emerging clinical and safety data. As a result of such a review or a recommendation by the Data Monitoring Committee (DMC), it may be necessary to stop the study before all subjects have completed the study. In addition, the Sponsor may terminate the study at an investigational site at any time (eg, 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 end of study (EOS) Visit.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at approximately 300 international study sites with experience in treating patients with compensated cirrhosis due to NASH. Prospective subjects will be identified primarily from the hospital and/or physician's database of patients with NASH or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international NASH patient societies, forums, or networks.

8.1.1. Subject Inclusion Criteria

1. Subjects ≥18 years of age
2. Subjects with a confirmed diagnosis of NASH and a fibrosis score of 4 based upon the NASH CRN scoring system determined by central reading of a liver biopsy obtained no more than 12 months before Day 1
3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Female subjects are considered as being of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   Effective methods of contraception are listed below (refer to Section 9.9 for highly effective contraceptive methods):

   - Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm with spermicide; or
   - Intrauterine device; or
   - Vasectomy (partner); or
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or
   - Abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse)
4. Must provide written informed consent and agree to comply with the study protocol

8.1.2. Subject Exclusion Criteria

Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization. For alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome), if the Screening Visit 2 value is ≥30% higher than the Screening Visit 1 value and > the upper limit of normal (ULN), then a third measurement must be obtained at an unscheduled visit. Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment:

1. Current or past history of a clinically evident hepatic decompensation event, such as ascites, variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes
2. Current or past history of hepatic function impairment with CP score ≥7 points

3. MELD score >12
4. Hospitalization within 1 year of Day 1 for complications of cirrhosis
5. Documented presence of varices based on prior endoscopy performed within 6 months of Day 1.
6. AST ≥5× ULN
    a. If a third serum AST measurement is required, and both Screening Visit 2 and unscheduled visit AST values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment
7. ALT ≥5× ULN
    a. If a third serum ALT measurement is required, and both Screening Visit 2 and unscheduled visit ALT values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment
8. Calculated creatinine clearance <60 mL/min using Cockcroft-Gault method
9. Platelet count ≤100 000/mm^3
10. Total bilirubin >2 mg/dL (except for subjects with an established diagnosis of Gilbert's syndrome, if hemoglobin and reticulocyte count are within normal range and conjugated bilirubin is <1.5× ULN)
    a. If a third serum total bilirubin measurement is required (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome), and both Screening Visit 2 and unscheduled visit values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment
11. Conjugated bilirubin ≥1.5x ULN
12. Albumin <3.5 g/dL
13. International normalized ratio (INR) ≥1.7
14. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before Day 1 (significant alcohol consumption is defined as more than 2 units/day for females and more than 4 units/day for males, on average)
15. Prior (at any point) or planned (during the study period) ileal resection, or prior (within 5 years before Screening) or planned (during the study period) bariatric surgery (eg, gastric bands, gastroplasty, Roux-en-Y gastric bypass)
16. Inability to safely undergo a liver biopsy
17. History of biliary diversion
18. Evidence of other known forms of chronic liver disease including:
    - Positive test result at Screening for hepatitis B surface antigen
    - Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening); or confirmed history of a positive HCV RNA test result(s)

except for subjects with evidence of spontaneous HCV eradication (defined as positive HCV antibodies at Screening, no history of positive HCV RNA result, and documentation that no anti-HCV therapy has been received)

- PBC, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome
- Alcoholic liver disease
- Wilson disease, hemochromatosis, or iron overload
- Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion)
- Prior known or suspected drug-induced liver injury within 5 years before Day 1
- Known or suspected HCC

19. History of liver transplant or current placement on a liver transplant waiting list
20. HbA1c ≥9.5% within 90 days before Day 1
21. LDL cholesterol ≥190 mg/dL and already on a stable dose of LDL-lowering medication for ≥30 days
22. LDL cholesterol <50 mg/dL (in subjects not on LDL-lowering medication)
23. Known positivity for human immunodeficiency virus infection
24. Subjects with recent history (within 1 year of Day 1) of significant atherosclerotic cardiovascular disease (ASCVD; myocardial infarction, unstable angina, acute coronary syndrome, cerebrovascular accident [stroke], cerebrovascular ischemia, transient ischemic attack, or peripheral vascular disease requiring intervention). Such subjects may be identified by different means, including, but not limited to, an abnormal 12-lead ECG, a history or planned cardiovascular intervention such as coronary revascularization (eg, percutaneous coronary intervention or coronary artery bypass graft), coronary angioplasty, stenting, carotid atherectomy, or placement of a cardiac pacemaker or defibrillator
    - Controlled hypertension without other recent manifestations of significant ASCVD and placement of cardiac pacemaker or defibrillator for reasons other than ASCVD (eg, for treatment of atrial fibrillation subsequent to nodal ablation) is not exclusionary
25. Current acute cholecystitis or acute biliary obstruction
26. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign carcinomas)
27. Known substance abuse in the year before Screening
28. Chronic use (≥12 months) of drugs historically associated with drug-induced NAFLD within the 5 years before Day 1 (eg, amiodarone, methotrexate, systemic glucocorticoids [unless used at physiologic replacement doses for the treatment of adrenal insufficiency], tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone

replacement, anabolic steroids [except for testosterone preparations used at physiologic replacement doses for the treatment of documented/confirmed hypogonadism], valproic acid, and other known hepatotoxins; see Section 9.4).

29. Pregnancy, planned pregnancy, potential for pregnancy (ie, unwillingness to use effective birth control during the study), or current or planned breast feeding
30. Participated in a clinical research study and received any active investigational product being evaluated for the treatment of diabetes, weight loss, or NASH in the 6 months before Day 1
31. Concurrent participation in any other interventional clinical trial.
32. Received any investigational product from Screening to Day 1, within 30 days before Day 1, or within 5 half-lives of the compound (whichever was longer) before Day 1
33. Previous exposure to OCA within 12 months of Day 1
34. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study, is uncertain
35. History of known or suspected clinically significant hypersensitivity to OCA or any of its components
36. Any other condition that, in the opinion of the Investigator, might confound the results, or would impede compliance or hinder completion of the study
37. ALP ≥1.5x ULN
38. History of known or suspected hypersensitivity to any ingredient in human albumin preparations (in the US where [redacted] is a study procedure).

8.2. Subject Withdrawal 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 are expected to continue in the study and should follow the regular visit schedule for the duration of the study phase (Double-Blind or OLE). Subjects who permanently discontinue from investigational product are expected to continue regular visit schedule for safety assessments until stabilization of the clinical event has occurred leading to discontinuation (per discretion of the Investigator and upon discussion with the medical monitor).

Refer to Section 7.7 for withdrawal criteria related to potential hepatic injury and/or decompensation; progression to cirrhosis with CP score ≥7; treatment-emergent acute or nonacute pancreatitis; ≥Grade 3 pruritus, AEs ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product; AEs ≥Grade 4 in severity and NOT or unlikely related to investigational product; liver transplantation, bariatric surgery, and pregnancy. Other reasons, including withdrawal of consent or lost to follow-up and withdrawal from [redacted] substudy, are described in Section 8.2.1 below.

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

Subjects who discontinue investigational product are expected to continue in the study until the end of the study. If a subject experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who discontinue investigational product prior to completion of the study need to also continue to follow the regular visit schedule through study completion (Month 18 for the Double-Blind Phase or Month 12 for the OLE phase). In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study completion. Early termination procedures should only be conducted if the subject withdraws consent (see Section 9.10.15).

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

- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject.
- Modification of consent:
  - Consent may be modified to discontinue study visits but allow periodic telephone contact of the subject (in line with the study visit schedule) through completion of the study (Month 18 if initiated in the Double-Blind Phase or Month 12 if initiated in the OLE phase), through the subject's primary care physician, or personal contacts who can provide information on behalf of the subject by the Investigator
  - Consent may be modified to discontinue study visits but allow continued access to medical records through completion of the study (Month 18 if initiated in the Double-Blind Phase or Month 12 if initiated in the OLE phase) to assess for potential MACE, and liver-related clinical outcomes
- Lost to Follow-Up
- Pregnancy
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important
- There is a major violation of the clinical study protocol
- The development of any exclusion criteria that might jeopardize safety (Section 8.1.2)

The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.

It is agreed that, for reasonable cause, either the Investigator or the Sponsor, may terminate this study.

8.2.1.2. 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 in the appropriate eCRF.

8.2.1.3. 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 in the appropriate eCRF.

8.2.1.4. Pregnancy

Whenever the site is notified of a possible pregnancy, the subject should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female subject becomes pregnant, the subject must stop taking investigational product immediately but will be encouraged to continue study visits until the end of the study. The subject must be followed by the Investigator through pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor. As described in Section 16.1.13, a pregnancy is not considered an AE for reporting purposes.

8.2.2. Reinitiating Investigational Product After Interruption

Prior to restarting investigational product after a prolonged interruption (ie, longer than 3 months [+2 weeks]), the subject must be reconsented and the procedures listed below must be performed before the subject re-starts investigational product regardless of the reason for interruption.

The following procedures will be performed to reinitiate investigational product:

- Review Informed Consent Form (ICF) and obtain signatures before performing the repeat baseline procedures
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and electronic case report form (eCRF)
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Record current concomitant medications
- Assess and record AEs
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Conduct physical exam
- Perform standard 12-lead ECG
- AUDIT, smoking habits, and caffeine consumption
- Health-related quality of life questionnaires and health status for the assessment of health utilities
- Perform hepatobiliary ultrasound for HCC screening unless data from a recent ultrasound (within 3 months) are available
- Obtain blood samples for:

  - HCC screening (alpha-fetoprotein [AFP])
  - Serum chemistry, hematology, and coagulation
  - Metabolic parameters
  - Lipoprotein analysis
  - Markers of inflammation, apoptosis, and necrosis
  - PD assessments
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class
  - Noninvasive scores of liver fibrosis (NAFLD fibrosis score [NFS], Fibrosis-4 [FIB-4], and aspartate aminotransferase to platelet ratio index [APRI])
  - Noninvasive panel of liver fibrosis (ELF and FibroMeter)
  - Cardiovascular risk scores (10-year ASCVD Risk, Framingham Risk Score [FRS], Reynolds score, SCORE)
- Noninvasive radiological liver fibrosis measurement (transient elastography [TE]; conducted at sites where device is available).
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Record the visit in the randomized and trial supply management system (RTSM) and dispense investigational product
- Administer investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

8.2.3. Subject Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any subject prematurely discontinues from the study. The date when the subject is withdrawn and the primary reason(s) for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. Subjects will be considered “lost to follow-up” only after reasonable, documented attempts to reach the subject prove unsuccessful.

In all cases, a reasonable effort must be made to determine the reason(s) that a subject fails to return for required study visits or discontinues from the study. This information must be documented in the eCRF.

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

The term investigational product (provided as part of this clinical study) refers to either OCA or placebo.

Three treatment groups will be evaluated:

- Placebo
- OCA (10 mg)
- OCA (10 mg → 25 mg)

Each dose will be made up of 1 tablet.

Investigational product will be taken orally with water, once daily for the duration of the study. Subjects will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time each day. Subjects must be instructed to swallow the tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the daily dose of investigational product is administered at the site, all assessments, except for the post-dose collection of blood samples for the subjects participating in the optional serial PK assessment and/or [redacted], must be completed before administration of investigational product.

Investigational product during the OLE Phase will be provided as open-label OCA tablets. The study will be blinded until the last subject completes the Double-Blind Phase and the database is locked.

9.2. Criteria for Uptitration

9.2.1. Double-Blind Phase (Month 3)

Subjects randomized to the OCA 10 mg → 25 mg arm in the Double-Blind Phase will receive OCA 10 mg for the first 3 months.

Prior to the Month 3 study visit, the Medical Monitor will perform a subject-level consolidated review of safety data, including data from the Month 1 and 2 study visits, as well as that from any unscheduled visit(s), for all study subjects. Case review and discussion with the Principal Investigator will occur as needed. The review will include but not be limited to the following:

- Liver-related adverse events

- Safety laboratories: chemistry panel including glucose, hematology panel, coagulation parameters; computed MELD score and CP score
- Physical examination (development of clinically evident ascites or manifestations of hepatic encephalopathy)

Additional considerations to determine the suitability to uptitrate will include an assessment of comorbid conditions, the subject's overall adverse event profile, concomitant medications with a focus on potentially hepatotoxic concomitant medications, and/or any new treatment(s) for comorbid condition(s). A subject may be considered for uptitration to OCA 25 mg if no safety and/or tolerability concerns are evident in the clinical judgement of the reviewer(s). If uptitration at Month 3 is not feasible, the window for uptitration may be extended by up to one calendar month, after consultation and agreement with the Medical Monitor. The uptitration review process is detailed in the study-specific Medical Management Plan.

Only those subjects who meet all of the following criteria will be eligible for uptitration at Month 3:

- Total bilirubin ≤1.2 mg/dL, serum albumin ≥3.5 g/dL, INR <1.5, and platelet count >100,000/mm^3 at baseline, and at all visits prior to Month 3 (including any unscheduled visits).
- Medical Monitor approval following a safety and tolerability assessment as described above.

Subjects who do not meet these criteria will not be uptitrated for the remainder of the study.

If at any time during the study, a subject who has undergone uptitration has total bilirubin >1.2 mg/dL, serum albumin <3.5 g/dL, INR ≥1.5, or platelet count ≤100,000/mm^3, the laboratory assessment(s) should be repeated within 7 days. If upon repeat evaluation, value(s) remain outside the specified criteria, investigational product should be downtitrated to a maximum daily dose of OCA 10 mg and the Medical Monitor should be notified promptly (see Table 5). Subjects randomized to the OCA 10 mg or placebo arms will undergo dummy titration to maintain study blind. All uptitration and downtitration will be implemented in a blinded fashion within RTSM to maintain the integrity of the study blind.

Dosing frequency post-titration may be temporarily decreased for tolerability reasons, following discussions with the Medical Monitor.

In addition, investigational product may be interrupted per safety criteria listed in Table 5 and Section 7.7. The procedures for re-initiating investigational product after prolonged interruption are provided in Section 8.2.2.

9.2.2. OLE Phase

Subjects who were randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg at entry into the OLE. Uptitration to OCA 25 mg at Month 3 in the OLE will be determined based on the same criteria and assessments employed in the Double-Blind Phase and described above. Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen.

All dosing, uptitration, and downtitration will be conducted in a blinded fashion in order to maintain the integrity of the study blind until all subjects complete the Double-Blind Phase and the database is locked.

9.3. Criteria for Extension of Double-Blind Treatment with Investigational Product

With the exception of sites in the Ukraine, for subjects who have been unable to complete the liver biopsy procedure at the Month 18 Visit due to the limitations caused by the COVID-19 pandemic and have or will run out of investigational product, investigational product may be extended beyond the Month 18 Visit for a maximum of 3 additional months of the double-blind period. In order for a subject to be eligible for this extension, the following must occur:

- Assessment of safety laboratory tests (chemistry panel including glucose, hematology panel, coagulation parameters; computed MELD score, and CP score) at Month 18, with review of results by the Medical Monitor and Investigator.
- Assessment of subject status at the Month 18 Visit must occur, either via an onsite study visit (if possible) or via a telemedicine visit ("virtual visit") as an alternative means of enabling Investigators and site staff to evaluate subject status and record any AEs or new medications. At a minimum, these visits must consist of a direct telephone or videocall discussion with the subject by the Investigator or an appropriate designee from the Investigator's team who is currently authorized to undertake examinations on the Investigator's Delegation of Authority Log. If an onsite visit or a telemedicine contact is not feasible (eg, no access to the subject) to assess status, investigational product will not be dispensed.
- If deemed necessary, additional assessment of safety laboratory tests and/or subject status may be performed at the discretion of the Investigator or Medical Monitor. Based on the individual subject-level safety and tolerability assessment, if both the Medical Monitor and the Investigator agree that the benefit-risk profile remains favorable, investigational product may be dispensed, which will provide an additional 3 months of treatment.

Unless all of the above measures occur, additional investigational product will not be provided.

9.4. Standard of Care and Concomitant Medications

Concomitant medications will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications taken before (ie, within 12 months of Day 1) and during the study must be recorded in the source documents and case report form, as well as any dose or dose regimen changes that occur during the study. All subjects will be questioned about concomitant medications at each clinic visit. To the extent possible, concomitant medications should be maintained at a stable dose throughout the study and at a minimum, from Day 1 through the end of the Double-Blind Phase, unless the baseline therapy is no longer considered clinically appropriate by the Investigator or the subject's primary care provider. In general, Investigators will be encouraged to follow guidelines for care

based upon local and institutional practice patterns and any relevant published practice guidelines.

Subjects must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 8) during the study. The restrictions related to use of drugs historically associated with drug-induced NAFLD are as follows:

- Drugs with Potential NASH-modifying Properties

  Subjects should either not be taking any drugs with potential NASH-modifying properties (specifically, TZDs/glitazones, vitamin E, or glucagon-like peptide-1 agonists) or be on a stable dose of these medications for 6 months before Day 1. Subjects providing historical biopsies to determine study eligibility should be on a stable dose of these medications for 12 months before Day 1 and these medications should not have been initiated after the historical liver biopsy was performed. Changes to these drugs with potential NASH-modifying properties are not permitted for the duration of the Double-blind Phase unless the baseline therapy is no longer considered clinically appropriate by the Investigator/or the usual care provider.

- Drugs with Potential NAFLD-inducing Properties

  Subjects chronically (≥12 months) using the following drugs that are historically associated with NAFLD will not be enrolled in the study if used within the 5 years before Day 1: amiodarone, methotrexate, systemic glucocorticoids [unless used at physiologic replacement doses for the treatment of adrenal insufficiency], tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids [except for testosterone preparations used at physiologic replacement doses for the treatment of documented hypogonadism], valproic acid, and other known hepatotoxins (refer to Exclusion Criterion 28; Section 8.1.2).

If a study subject receives a COVID-19 vaccination, the date(s) of vaccination, vaccine name, and manufacturer should be recorded as a concomitant medication for each dose (refer to Section 10).

9.4.1. LDL-Lowering Medications

Appendix A provides a general guidance for cholesterol management including monitoring, triggers for intervention, and treatment goals. Use of LDL-lowering medications (eg, simvastatin, atorvastatin, PCSK9 inhibitors) should be at a stable dose ≥30 days before Day 1. During the study, changes to LDL-lowering medication regimen are allowed, given the potential increase in total and LDL cholesterol following treatment with OCA.

9.4.2. Warfarin

Taken concomitantly, OCA and warfarin may decrease INR, thus INR should be monitored and the dosage of warfarin adjusted, as needed, to maintain the target INR range.

9.4.3. Bile Acid Sequestrants

Bile acid sequestrants (BAS) have the potential to bind to fat-soluble vitamins, hormones, or medications. Subjects taking BAS (including colestyramine and its derivatives, colestipol, colesevelam, or other BAS) or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product in temporal relationship to these agents, ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (ie, BAS should be administered 4 hours before or 4 hours after investigational product administration). For guidance on using BAS to treat pruritus ≤Grade 2 in severity refer to Section 16.1.6.1.

Due to the potential of BAS to affect the disposition of OCA, long-term use of BAS should be avoided where possible while taking investigational product. In subjects taking long-term BAS for other medical conditions (eg, hypercholesteremia), other therapies to replace the BAS should be considered.

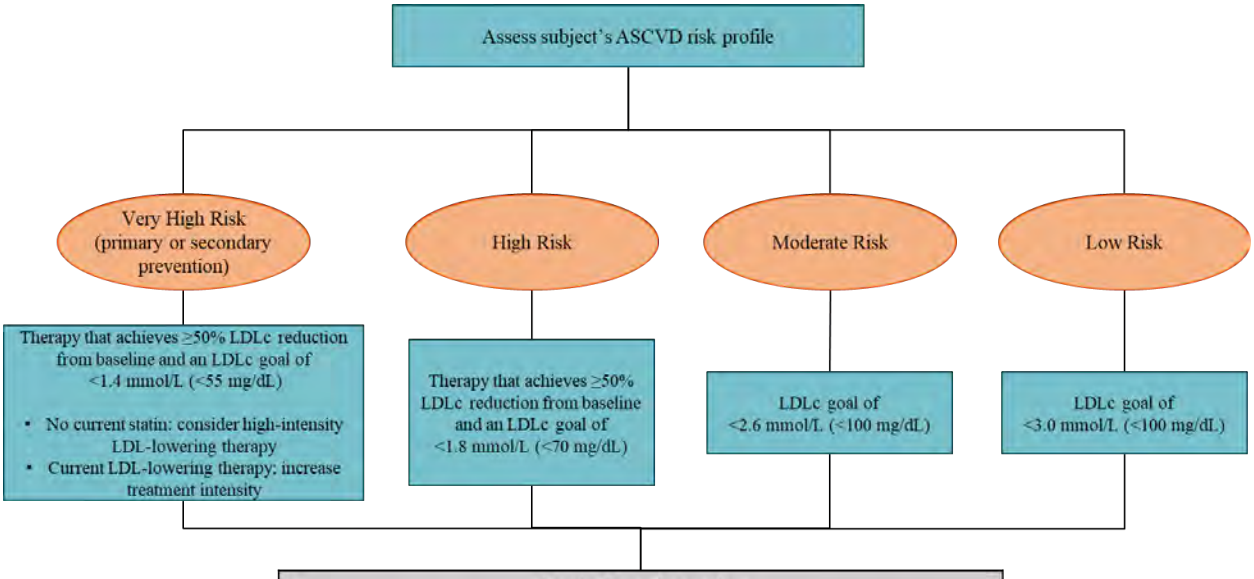
9.4.4. Drug-Drug Interaction

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate, showed a weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

9.4.5. Standard of Care: Management of Dyslipidemia

Given the prevalence of dyslipidemia in patients with NASH and the potential increase in total cholesterol and LDLc following treatment with OCA, it is recommended that Investigators proactively monitor and manage lipid levels in all subjects as indicated via appropriate medicinal interventions (eg, statins). Recent guidelines stress the importance of evaluating ASCVD risk in all patients to help guide decisions in recommending therapies and reducing LDLc to reduce the risk and prevent onset or recurrence of ASCVD. As such, reducing lipids, particularly LDLc, are part of a comprehensive CV risk reduction strategy. Results from meta-analyses have confirmed the dose-dependent reduction in ASCVD with LDLc-lowering agents; the greater the absolute LDLc reduction, the greater the CV risk reduction. Recent guidelines for the management of lipids, such as the 2019 ESC/EAS Guidelines (Mach 2020), suggest that LDLc targets should be individualized based on available treatments and each subject's overall ASCVD risk profile. The targeted approach to lipid management is aimed at reducing atherosclerotic risk by substantially lowering LDLc to levels that have been achieved in recent large-scale trials (Figure 4).

Figure 4: Therapeutic Targets for LDLc Based on Subject ASCVD Risk



Statin Dose Intensity			
Drug Name	**High Intensity Dose**	**Moderate Intensity Dose**	**Low Intensity Dose**
Atorvastatin	40 – 80 mg	10 – 20 mg	--
Rosuvastatin	20 – 40 mg	5 – 10 mg	--
Simvastatin	--	20 – 40 mg	10 mg
Pravastatin	--	40 – 80 mg	10 – 20 mg
Lovastatin	--	40 – 80 mg	20 mg
Fluvastatin XL	--	80 mg	--
Fluvastatin	--	40 mg BID	20 – 40 mg
Pitavastatin	--	1 – 4 mg	--

Adapted from: 2019 ESC/EAS guidelines (Mach 2020).

9.4.6. Standard of Care: Management of Hyperglycemia

Subjects with type 2 diabetes mellitus and those who are at risk for developing hyperglycemia should be closely monitored throughout the study in order to ensure appropriate therapeutic interventions based on current guidelines to mitigate potential elevations of serum glucose and initiate them when indicated. The Investigator should proactively consider major risk factors for developing hyperglycemia that include family history of type 2 diabetes; obesity; African American, Native American, Hispanic or Asian American heritage; hypertension; dyslipidemia; or history of gestational diabetes. Early signs and symptoms of hyperglycemia that include polyuria, polydipsia, polyphagia, blurred vision, fatigue and headaches should also be monitored.

Subjects who experience treatment-emergent hyperglycemia should be closely monitored and treatment should be based on current guidelines. Initiation of therapy should take into consideration each subject's underlying health status and the use of appropriate glycemic targets.

The management of hyperglycemia depends on several factors including: the duration, frequency and severity of hyperglycemia, and the subject's age, health, and cognitive function. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have updated their recommendations on the management of hyperglycemia based on

underlying risk factors including underlying cardiovascular and renal disease. According to these guidelines, glycemic treatment targets should be individualized based on patient preferences and goals, risk of adverse effects of therapy (eg, hypoglycemia and weight gain), and subject characteristics, including frailty and comorbid conditions (Davies 2018). Glycemic management is primarily assessed by measuring HbA1c and the choice of glucose-lowering medications should be accompanied by lifestyle management, weight loss, exercise, dietary modification, diabetes self-management education and support, and patient-centered care.

While criteria for initiating therapy requires individualizing HbA1c targets, a reasonable HbA1c target is approximately ≤7% (53 mmol/mol) (Davies 2018). The selection of the appropriate individualized therapy is described in current guidelines from ADA and EASD for management of hyperglycemia (Appendix B).

Subjects displaying increasing fasting glucose, HBA1c, or HOMA-IR levels should be referred to either their treating physician, if already under care for diabetes, or to their HCP or an endocrinologist if they experience new onset type 2 diabetes mellitus.

9.5. Treatment Compliance

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

Subjects should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the indicated visits in Table 1 and Table 2. The Investigator or designee should perform investigational product accountability (ie, 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.

9.6. Randomization and Blinding

9.6.1. Methods of Assigning Subjects to Treatment Groups

This study will be conducted in a double-blind, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo. Randomization will be done using an RTSM and will be based on a predefined randomization code generated by the Sponsor or designee. Subjects randomized to OCA 10 mg → 25 mg will initiate dosing at OCA 10 mg for 3 months prior to uptitrating to OCA 25 mg. Uptitration will be determined based on the laboratory criteria and safety and tolerability assessments completed prior to Month 3 (Section 9.2.1).

Randomization of subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no).

All subjects who enroll into the OLE will receive OCA. Subjects randomized to placebo in the Double-Blind Phase will be re-randomized to OCA 10 mg or OCA 10 mg → 25 mg arms, with uptitration at OLE Month 3 in the OCA 10 mg → 25 mg arm (refer to Section 9.2)

The RTSM will also serve as the investigational product inventory and management system.

The Investigator or designee will be required to register the subject in the RTSM and may be prompted to provide patient data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind.

To maintain blinding, all placebo, OCA 10 mg, and OCA 25 mg tablets and bottles will be identical.

9.6.2. Blinding

The subjects, Investigators, and study site staff will be blinded to the subject's treatment regimen until all subject data have been collected from the study and the database is locked for Double-Blind Phase. Using this approach, blinding of the study will be maintained.

9.6.3. Emergency Unblinding Procedures

Randomization codes and corresponding treatment assignments will be made available to the Investigator for emergency use only through the RTSM system. When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the unblinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case in the subject's source record. Subsequently, the Investigator should contact the Medical Monitor to explain any premature unblinding of treatment assignment (eg, accidental unblinding or unblinding due to a SAE). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for the purpose of evaluating an emergent safety issue or for regulatory reporting purposes, the Medical Monitor will document within study correspondence the rationale, circumstances, and the person(s) being informed about the unblinding.

The DMC (refer to Section 17.13) will have access to randomization and will be able to review the cases of premature unblinding. The DMC will document details about any subject who was unblinded in the closed session DMC minutes, which will be made available to the Sponsor only after the double-blind database is locked and unblinded. Cases of premature unblinding (as noted above) will be reviewed by the DMC.

Access to randomization codes and corresponding treatment assignments will also be made available through the RTSM system to the appropriate, named individual(s) responsible for unblinding suspected unexpected serious adverse reactions (SUSARs) for reporting to the regulatory authorities.

9.7. Assignment of Site and Subject Numbers

9.7.1. 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.

9.7.2. Subject Numbers

Subjects are assigned using a unique 10-character, 9-digit identifier (AAA-BBBCCC), independent of the randomization number. The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits represent the site number (BBB). The last 3 digits represent a unique screening number that is assigned in sequential order at each site starting with 001 (CCC). Note, in the case of incorrect data entry by a site when more than one subject is inadvertently created, the spurious subject numbers will be deleted and may not be used again; in this circumstance there may be gaps in the subject numbering scheme at a site.

9.8. Restrictions

No additional restrictions.

9.9. Highly Effective Contraception

Recent guidelines recommend “highly effective” contraception measures for investigational products with limited or no human data available on pregnancies. (HMA CTFG 2014). Highly effective methods of contraception per the CTFG guidelines are those that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly. The highly effective contraception measures should be maintained during treatment and until the end of relevant systemic exposure. Women of child-bearing potential, currently enrolled in the 747-304 study, will employ the highly effective contraception measures during treatment with IP for their participation in the study.

Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use at least one highly effective method of contraception during the study and for 30 days after the end of treatment.

Highly effective methods of contraception include the following:

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy (male partner)
- Combined (estrogen- and progestogen-containing) hormonal contraception (eg, oral, intravaginal or transdermal) associated with inhibition of ovulation.

- Progestogen-only hormonal contraception (eg, oral, injectable or implantable) associated with inhibition of ovulation.
- Sexual abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).

9.10. Visit Procedures

Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. The day of the first dose from the OLE bottle is considered OLE Day 1. If Day 1 occurs on January 1st, Month 3 should ideally occur on April 1st (±1 week). This is the definition of a calendar month. The visit windows are listed in Table 1 and Table 2. Acceptable windows for PK sampling timepoints are in Table 7.

9.10.1. 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. Subjects will also be required to provide consent prior to participating in any of the optional assessments, such as providing blood samples for serial PK draws.

9.10.2. Fasting Requirement at Study Visits

Starting with Screening Visit 2, all subjects must arrive to the study site in a fasted state (at least 8 hours before each visit). Water is permitted during the fasting period. If the subject reports having eaten within 8 hours of the visit, the nonfasted state will be documented in the source; however, scheduled assessments (blood collection) will still be performed during the visit, and these subjects will be reminded that fasting is required before all study visits.

9.10.3. Screening Visit Procedures

Two Screening Visit assessments must be performed to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months have elapsed from the date of their most recent screening visit procedure, or with alternative timing approved by the Sponsor's Medical Monitor; however, all Screening procedures (including obtaining informed consent) should be repeated and a new three-digit Screening number assigned.

The 2 Screening visits must occur at least 4 weeks apart to confirm pretreatment serum chemistry levels, including ALT, AST, and total bilirubin.

- Screening Visit 1 will occur ≤12 weeks prior to Day 1.
- Screening Visit 2 will occur ≥4 weeks after Screening Visit 1.

If ALT, AST, or total bilirubin (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome) assessments collected at Screening Visit 2 is are ≥30% higher than the Screening Visit 1 value(s) and >ULN, then a third measurement must be obtained at an unscheduled visit for eligibility determination.

9.10.3.1. Screening Visit 1

The Screening Visit assessments must be performed within ≤12 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study.

If an Investigator intends to rescreen a subject <2 months after the initial screening, this decision should be discussed with the Sponsor's Medical Monitor to confirm that early rescreening will not affect safety or efficacy for the subject. When rescreening, all Screening Visit procedures should be repeated and a new screening number assigned. Subjects should be reconsented, as appropriate, at this time.

Screening Visit 1 procedures for all subjects are as follows:

- Review ICF and obtain signatures before performing any study-related procedures, including Screening procedures
- Collect medical history
- Assess and record any pretreatment AEs (after the ICF has been signed)
- Record prior (if within 12 months of Day 1) and current concomitant medications
- Verify inclusion and exclusion criteria for eligibility
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Measure height. Record weight and BMI
- Conduct physical exam
- Perform standard 12-lead ECG
- Determine alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT] questionnaire)
- Perform hepatobiliary ultrasound for HCC screening and gallbladder assessment unless data from a recent historic ultrasound (within 3 months of Day 1) are available
- Perform esophagogastroduodenoscopy (EGD) procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with endoscopic evidence of varices will not be enrolled in the study.
- Assess availability of liver biopsy samples obtained ≤12 months prior to Day 1, for which unstained slides can be prepared and submitted for central review. All samples

must be submitted for central read such that the report is available prior to Day 1. For subjects without a recent liver biopsy with unstained slides or adequate tissue block, an on-study liver biopsy must be performed within the 12-week screening window before Day 1 (assuming all other Screening assessments indicate a likelihood that the subject will qualify based on biopsy).

- Obtain blood samples for:
  - HCC screening (AFP)
  - Serum chemistry, hematology, and coagulation
  - Glucose and HbA1c
  - Virology Screen (HCV and hepatitis B surface antigen [HBsAg])
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
- Noninvasive radiological liver fibrosis measurements (TE and MRE; conducted at sites where device is available; MRE only in subjects enrolled prior to Version 5 of the protocol and not in newly enrolled subjects)

  Note: Noninvasive radiological measurements may be completed any time during Screening Visit 1 through Day 1 but should be conducted prior to an on-study liver biopsy, if one is necessary, and before initiation of investigational product on Day 1.
- Obtain urine sample for urinalysis
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted). Fasting is required before Screening Visit 2.

9.10.3.2. Screening Visit 2

Screening Visit 2 procedures must be performed ≥4 weeks after Screening Visit 1 and are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Medical history
- Record prior (if within 12 months of Day 1) and current concomitant medications

- Assess and record any pretreatment AEs
- Verify inclusion and exclusion criteria for eligibility
- Measure circumference of waist and hips
- If not conducted at Screening Visit 1, noninvasive radiological liver fibrosis measurements (TE and MRE; conducted at sites where device is available; MRE only in subjects enrolled prior to Version 5 of the protocol and not in newly enrolled subjects)

  Note: Baseline noninvasive radiological measurements should be conducted prior to an on-study liver biopsy
- For subjects without a recent liver biopsy with unstained slides or adequate tissue block (≤12 months prior to Day 1), collect liver biopsy sample. (Procedure may be performed within the 12-week screening window, and assuming all other Screening assessments indicate a likelihood that the subject will qualify based on biopsy).
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
- Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
- Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted)

9.10.4. Day 1 Procedures (Randomization)

All Day 1 procedures, except for the [redacted], should be done before dosing. Day 1 Visit procedures for all subjects are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Record prior and current concomitant medications
- Assessment of baseline pruritus (via medical history evaluation)
- Assess and record any pretreatment AEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation

  - Intercurrent illness and/or potential adverse events (Appendix C)
- Verify inclusion and exclusion criteria for eligibility
- Randomize the subject only if s/he meets all inclusion criteria and no exclusion criteria
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Conduct physical exam
- Perform standard 12-lead ECG
- AUDIT, smoking habits, and caffeine consumption
- Health-related quality of life questionnaires and health status for the assessment of health utilities
- Pruritus VAS
- If a hepatobiliary ultrasound for HCC screening and gallbladder assessment was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound
- Obtain blood samples for:
  - HCC screening (AFP)
  - Serum chemistry, hematology, and coagulation
  - Free fatty acids
  - Thyroid hormones
  - Glucose and HbA1c
  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
  - Lipoprotein analysis
  - Markers of inflammation, apoptosis, and necrosis
  - PD assessments (all subjects)
  - Exploratory biomarkers of disease severity
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Noninvasive panel of liver fibrosis (ELF and FibroMeter)

  - Cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, SCORE)
- Noninvasive radiological liver fibrosis measurements (TE and MRE; conducted at sites where device is available) if not conducted during Screening. (MRE only in subjects enrolled prior to Version 5 of the protocol)
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- [redacted]
- Record the visit in RTSM and dispense investigational product
- Administer the first daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.5. DB Month 1 Procedures

All procedures, except for the post-dose collection of blood samples for subjects participating in the PK assessments, should be completed before dosing, including trough PK sampling.

Month 1 Visit procedures for all subjects are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect the bottle of investigational product dispensed on Day 1, assess subject's investigational product compliance, and perform investigational product accountability
- Record current concomitant medications
- Assess and record any TEAEs

- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Health-related quality of life questionnaires and health status for the assessment of health utilities
- Pruritus VAS
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - Glucose
  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
  - Markers of inflammation, apoptosis, and necrosis
  - Trough PK assessment (all subjects)
  - PD assessments (all subjects)
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Potential DILI management algorithm (liver biochemistry)
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Record the visit in RTSM; there is no dispensing of investigational product via RTSM at this visit.
- If subject is not participating in serial PK assessments, administer the daily dose of investigational product from the bottle dispensed on Day 1 at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet. Return the same bottle of investigational product to the subject to continue daily dosing at home.
- If subject consented to participate in serial PK assessment, the following procedures will be conducted:
  - Dispense/Administer investigational product from the double-blind bottle (collected from the subject upon arrival for this visit) with 240 mL (8 oz.) of

water. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.

- Collect blood samples at: 0.5, 0.75, and 1-hour postdose
- Immediately following 1-hour post-dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
- Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose

Note: Subjects should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Subjects should not drink any water until at least 1-hour postdose. Refer to Section 14.1 for complete information and instructions regarding serial PK assessments.

- Return the bottle of investigational product that was dispensed to the subject to continue daily dosing at home.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.6. DB Month 2, Month 5, Month 9, and Month 15 Procedures

All Month 2, Month 5, Month 9, and Month 15 procedures should be done before dosing. Visit procedures for all subjects are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)

- Record weight and BMI
- Measure circumference of waist and hips
- Pruritus VAS
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - Glucose (Months 2, 5, 9, and 15) and HbA1c (Month 9 and Month 15 only)
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Potential DILI management algorithm (liver biochemistry)
- Perform a urine-based-hCG pregnancy test for females of childbearing potential
- For Month 2 and Month 5, record the visit in RTSM; there is no dispensing of investigational product via RTSM at this visit.
- For Month 9 and Month 15, record the visit in RTSM and dispense a new bottle of investigational product.
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- For Month 2 and Month 5, return the bottle of investigational product that was dispensed to the subject to continue daily dosing at home.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.7. DB Month 3 Procedures

All Month 3 procedures, except for the [redacted], should be done before dosing, including trough PK sampling. Visit procedures for all subjects are as follows:

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

  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Health-related quality of life questionnaires and health status for the assessment of health utilities
- Pruritus VAS
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - Glucose and HbA1c
  - Markers of inflammation, apoptosis, and necrosis
  - Trough PK assessment (all subjects)
  - PD assessments (all subjects)
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive panel of liver fibrosis (ELF and Fibrometer)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Potential DILI management algorithm (liver biochemistry)
- Perform a urine-based-hCG pregnancy test for females of childbearing potential
- [redacted]

[redacted]

- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.8. DB Month 4 Procedures

All Month 4 procedures, except for the post-dose collection of blood samples for subjects participating in the PK assessments, should be done before dosing, including trough PK sampling. Visit procedures for all subjects are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Pruritus VAS
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation

  - Glucose only
  - Markers of inflammation, apoptosis, and necrosis
  - Trough PK assessment (all subjects)
  - PD assessments (all subjects)
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Potential DILI management algorithm (liver biochemistry)
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Record the visit in RTSM; there is no dispensing of investigational product via RTSM at this visit.
- If subject consented to participate in serial PK assessment, the following procedures will be conducted:
  - Dispense/Administer investigational product from the double-blind bottle (collected from the subject upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 0.5, 0.75, and 1-hour post-dose
  - Immediately following 1-hour post-dose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose

  Note: Subjects should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Subjects should not drink any water until at least 1-hour postdose. Refer to Section 14.1 for complete information and instructions regarding serial PK assessments.
- For subjects not participating in serial PK collection, administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Return the bottle of investigational product that was dispensed to the subject to continue daily dosing at home.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic

- To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.9. DB Month 6 and Month 12 Procedures

All Month 6 and Month 12 procedures, except for the post-dose collection of blood samples for subjects participating in the PK and/or [redacted], should be done before dosing, including trough PK sampling. Visit procedures for all subjects are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- AUDIT, smoking habits, and caffeine consumption
- Health-related quality of life questionnaires and health status for the assessment of health utilities
- Pruritus VAS
- Noninvasive radiological liver fibrosis measurements (TE and MRE; conducted at sites where device is available); Month 6 only (MRE only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects)
- Perform hepatobiliary ultrasounds for HCC screening and gallbladder assessment
- Obtain blood samples for:
  - HCC screening (AFP)
  - Serum chemistry, hematology, and coagulation
  - Free fatty acids
  - Glucose and HbA1c

  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
  - Lipoprotein analysis
  - Thyroid hormones (Month 6 only)
  - Markers of inflammation, apoptosis, and necrosis
  - Trough PK assessment (all subjects)
  - PD assessments (all subjects)
  - Exploratory biomarkers of disease severity (Month 6 only)
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Noninvasive panel of liver fibrosis (ELF and FibroMeter)
  - Potential DILI management algorithm (liver biochemistry)
  - Cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, SCORE) (Month 12 only)
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- [redacted]
- Record the visit in RTSM and dispense a new bottle of investigational product.
- For Month 6, administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- For Month 12, if subject consented to participate in serial PK assessment, the following procedures will be conducted:
  - Dispense/Administer investigational product with 240 mL (8 oz) of water. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
  - Collect blood samples at: 0.5, 0.75, and 1-hour post-dose
  - Immediately following 1-hour post-dose blood draw, administer meal replacement drink (to be consumed within 5 to 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose

Note: Subjects should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Subjects should not drink any water until at least 1-hour postdose. Refer to Section 14.1 for complete information and instructions regarding serial PK assessments.

- For Month 12, if subjects are not participating in serial PK collection, administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.10. DB Month 18/EOT/EOS/OLE Day 1 Visit for Subjects Continuing into the OLE

For subjects who are unable to complete the liver biopsy procedure at the Month 18 Visit due to the limitations caused by the COVID-19 pandemic and have or will run out of investigational product, investigational product may be extended beyond the Month 18 Visit for a maximum of 3 additional months of the double-blind period (refer to Section 9.3 for requirements of this extension). Regardless of whether these subjects are eligible for the additional supply of investigational product, they are to return to the site for an unscheduled visit to complete the liver biopsy (and other procedures assessments as required) as soon as practical following lifting/easing of the COVID-19 restrictions (refer to Section 9.10.16 for details of this visit).

All Month 18/EOT/EOS procedures, except for the post-dose collection of blood samples for subjects participating in the PK and/or [redacted], should be done before dosing, including trough PK sampling.

Visit procedures for all subjects are as follows:

- When a subject completes the Double-Blind Month 18 Visit and decides not to continue participation in the OLE, the data will be recorded as EOS procedures in the eCRF
- When a subject discontinues investigational product during the Double-Blind Phase but continues with regularly scheduled study visits, the visit data will be recorded as EOT procedures in the eCRF and the subject's final study visit will be recorded as EOS procedures in the eCRF. The EOT visit procedures listed below must be performed as close as possible to the subject's last dose of investigational product. Subsequent study visit data will be recorded in the visit-specific eCRF.
- If a subject will be entering the OLE phase, the Double-Blind Month 18 Visit and the Day 1 OLE Visit should be combined as a single visit
- Verify that the subject has fasted for at least 8 hours

  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Conduct physical exam
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Perform standard 12-lead ECG
- AUDIT, smoking habits, and caffeine consumption
- Health-related quality of life questionnaires and health status for the assessment of health utilities
- Pruritus VAS
- Noninvasive radiological liver fibrosis measurements (TE and MRE; conducted at sites where device is available; MRE only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects)
- Perform hepatobiliary ultrasounds for HCC screening and gallbladder assessment
- Liver biopsy (must be completed prior to dosing with investigational product at Day 1 OLE). When a subject completes a liver biopsy as part of the EOT visit during the Double-Blind Phase, and remains in the study, a second biopsy is not required at the Month 18 Visit. Refer to Section 9.10.16 for guidance for subjects unable to complete the Month 18 biopsy due to COVID-19 restrictions.
- Obtain blood samples for:
  - HCC screening (AFP)
  - Serum chemistry, hematology, and coagulation
  - Free fatty acids
  - Glucose and HbA1c

  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
  - Lipoprotein analysis
  - Thyroid hormones
  - Markers of inflammation, apoptosis, and necrosis
  - Trough PK assessment (all subjects)
  - PD assessments (all subjects)
  - Exploratory biomarkers of disease severity
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, and SCORE)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Noninvasive panel of liver fibrosis (ELF and FibroMeter)
  - Potential DILI management algorithm (liver biochemistry)
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- [redacted]
- If subject consented to participate in serial PK assessment, the following procedures will be conducted:
  - Collect blood samples at: 0.5, 0.75, and 1-hour postdose
  - Immediately following 1-hour postdose blood draw, administer meal replacement drink (to be consumed within 5 – 10 minutes)
  - Collect blood samples at: 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose

  Note: Subjects should not consume any food for the duration of the 6-hour PK assessments except the meal replacement drink. Subjects should not drink any water until at least 1-hour postdose. Refer to Section 14.1 for complete information and instructions regarding serial PK assessments.

9.10.10.1. Additional Procedures at DB Month 18/OLE Day 1 Visit for Subjects Continuing into the OLE

Subjects who continue into the OLE Phase after completing the procedures listed for the Month 18 Visit (Section 9.10.10) will undergo the following procedures:

- Review OLE ICF and obtain signatures before performing any OLE-specific procedures. The OLE ICF may be obtained as early as the Month 15 study visit in the Double-Blind Phase.
- Perform EGD procedure unless data from a recent EGD (within 6 months of OLE Day 1) are available. Subjects with endoscopic evidence of varices will not continue in the OLE Phase.
- Subjects randomized to placebo during the DB Phase will be re-randomized to OCA 10 mg or OCA 10 mg → 25 mg arms on OLE Day 1; the placebo subjects in the OCA 10 mg → 25 mg arm will receive OCA 10 mg for 3 months followed by OCA 25 mg in the OLE, as described in Section 9.2.2. Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the treatment they were assigned.
- Record the visit in RTSM, and dispense investigational product
- Administer investigational product from the double-blind bottle issued at previous visit (collected from the subject upon arrival for this visit) with 240 mL (8 oz.) of water. Instruct the subject to swallow the tablet whole; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions and advise the subject:
  - To take the first dose of OLE investigational product the next day. The day of the first dose from the OLE bottle is considered OLE Day 1.
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) prior to the next visit but water is permitted.

9.10.11. OLE Month 1

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits

- Collect used bottles of investigational product dispensed at previous visit, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - Glucose
  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Potential DILI management algorithm (liver biochemistry)
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Record the visit in RTSM; there is no dispensing of investigational product via RTSM at this visit.
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Return the bottle of investigational product that was dispensed to the subject at OLE Day 1 to continue daily dosing at home.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic

- To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.12. OLE Months 2, 3, 4, 5, 9

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product dispensed at previous visit, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Obtain blood samples for:
  - Serum chemistry, hematology, and coagulation
  - Glucose at Months 2, 3, 4, 5, and 9 and HbA1c at Months 3 and 9
  - Lipoprotein analysis (Month 2 and Month 5 only)
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Noninvasive panel of liver fibrosis (ELF and Fibrometer) (Month 3 only)
  - Potential DILI management algorithm (liver biochemistry)
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Record the visit in RTSM and
  - Dispense a new bottle of investigational product (Month 3 and 9).

  - Return the bottle of investigational product that was previously dispensed to the subject to continue daily dosing at home (Months 2, 4 and 5).
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.13. OLE Month 6

All procedures should be done before dosing.

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product dispensed at previous visit, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- AUDIT, smoking habits, and caffeine consumption
- Perform hepatobiliary ultrasound for HCC screening
- Obtain blood samples for
  - HCC screening (AFP)

  - Serum chemistry, hematology, and coagulation
  - Free fatty acids
  - Lipoprotein analysis
  - Glucose and HbA1c
  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
  - Thyroid hormones
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Noninvasive panel of liver fibrosis (ELF and Fibrometer)
  - Potential DILI management algorithm (liver biochemistry)
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Noninvasive radiological liver fibrosis measurements (TE; conducted at sites where device is available;)
- Record the visit in RTSM and dispense a new bottle of investigational product
- Administer the daily dose of investigational product at the study site. Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - Take the investigational product at approximately the same time each day
  - NOT to take investigational product on the morning of the next visit
  - To bring the investigational product bottle(s) with them to his/her next visit; s/he will dose at the clinic
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted

9.10.14. OLE Month 12/EOT/EOS

- When a subject completes the OLE Month 12 Visit, the data will be recorded in the Month 12 and EOS eCRFs.
- When a subject discontinues investigational product but continues with regularly scheduled study visits during the OLE phase, the data will be recorded as EOT procedures in the eCRF and the subject's final study visit will be recorded as EOS procedures in the eCRF. The EOT visit procedures listed below must be performed

as close as possible to the subject's last dose of investigational product. Subsequent study visit data will be recorded in the visit-specific eCRF.

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product dispensed at previous visit, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of:
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)
- Record weight and BMI
- Measure circumference of waist and hips
- Conduct physical exam
- Perform standard 12-lead ECG
- AUDIT, smoking habits, and caffeine consumption
- Perform hepatobiliary ultrasound for HCC screening
- Obtain blood samples for:
  - HCC screening (AFP)
  - Serum chemistry, hematology, and coagulation
  - Free fatty acids
  - Lipoprotein analysis
  - Glucose and HbA1c
  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
  - Thyroid hormones
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score

  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, and SCORE)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)
  - Noninvasive panel of liver fibrosis (ELF and Fibrometer)
  - Potential DILI management algorithm (liver biochemistry)
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Noninvasive radiological liver fibrosis measurements (TE; conducted at sites where device is available)
- Liver biopsy (optional)

9.10.15. Early Termination Procedures

Early Termination procedures will be required whenever a subject discontinues treatment with investigational product and will not continue with regularly scheduled study visits. The ET visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product.

The data will be recorded as EOS procedures in the eCRF.

Early Termination procedures for subjects who discontinue during Double-Blind or OLE Phase are as follows:

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and eCRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits
- Collect used bottles of investigational product, assess subject's investigational product compliance, and perform investigational product accountability
- Review and record current concomitant medications
- Assess and record any TEAEs
- Assess signs and symptoms of
  - Hepatic injury or decompensation
  - Intercurrent illness and/or potential adverse events (Appendix C)
- Conduct physical exam
- Record vital signs (body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes)

- Record weight and BMI
- Measure circumference of waist and hips
- Perform standard 12-lead ECG
- AUDIT, smoking habits, and caffeine consumption
- Perform hepatobiliary ultrasounds for HCC screening
- Obtain blood samples for
  - HCC screening (AFP)
  - Serum chemistry, hematology, and coagulation
  - Free fatty acids
  - Thyroid hormones
  - Glucose and HbA1c
  - Insulin, C-Peptide, HOMA-β, and HOMA-IR
- Calculations will be performed by the Sponsor or designee for:
  - MELD Score
  - CP Score/Class (assessment of ascites and hepatic encephalopathy is required)
  - Cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, and SCORE)
  - Potential DILI management algorithm (liver biochemistry)
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Liver biopsy (optional)

The following Early Termination procedures will be performed only in Double-Blind Phase:

- Health-related quality of life questionnaires (eg, patient reported outcomes) and health status for the assessment of health utilities (eg, healthcare resource use)
- Pruritus VAS
- Noninvasive radiological liver fibrosis measurements (TE and MRE; conducted at sites where device is available; MRE only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects)
- Obtain blood samples for
  - Lipoprotein analysis
  - Markers of inflammation, apoptosis, and necrosis
  - Trough PK assessment (all subjects)

- PD assessments (all subjects)
- Exploratory biomarkers of disease severity

- Calculations will be performed by the Sponsor or designee for:
  - Noninvasive panel of liver fibrosis (ELF and FibroMeter)
  - Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI)

9.10.16. Unscheduled Safety Visit

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

Additionally, all subjects who were unable to complete the liver biopsy at the Month 18 Visit due to the restrictions from the COVID-19 pandemic, regardless of whether they received additional supply of investigational product or not as described in Section 9.3, are to return to the site for an unscheduled visit to complete the liver biopsy as soon as practical following lifting/easing of the COVID-19 restrictions. At this unscheduled visit, the types of procedures/assessments required to be performed, in addition to the liver biopsy, are the following:

- If this unscheduled visit occurs more than 6 weeks since the original Month 18 Visit, then all Month 18 study visit procedures are to be performed, including but not limited to procedures that could not be performed at Month 18 due to COVID-19 restrictions.
- If this unscheduled visit occurs within 6 weeks since the original Month 18 Visit, then only the assessments that could not be obtained at the Month 18 Visit and recording of any AEs and concomitant medications are to be completed.
- In addition, for any subject who wishes to enroll in the OLE phase, safety laboratory tests (refer to Table 2) as well as any additional assessments required to determine eligibility for the OLE (including EGD) are to be completed.

10. STUDY MANAGEMENT DURING COVID-19

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

This section describes the processes under which subjects who are unable or unwilling to return to study sites may complete protocol-specified assessments and continue to receive investigational product until in-person site visits can resume. To ensure the continued safety monitoring of the participating subject and to minimize the potential adverse impact on achieving the objectives of the study due to the restrictions from the COVID-19 pandemic, the

following approaches may be applied to the study protocol. Investigators should document the reason for any contingency measures implemented and how restrictions related to COVID-19 led to the changes in study conduct, duration of those changes, and how those study participants were impacted.

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

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

- Subject Consent: If re-consent is necessary alternative ways of obtaining re-consent should be considered, including obtaining oral consent via phone or video-call supplemented with e-mail confirmation. If the technology is available, then electronic methods of obtaining informed consent such as DocuSign® would also be considered.
- Subject Assessment: In place of in-person visits, assessment of subjects may be performed using a "virtual visit" including phone consultation, or video (telemedicine) visits by authorized investigators to undertake examinations on the study. All assessments should adhere as closely as possible to the visit windows specified in the protocol schedule of visits. In case this is not possible, please discuss with the Medical Monitor or Sponsor.
- Laboratory Tests: If central laboratory testing cannot be performed at the study site or via homecare visits, every attempt should be made to perform the protocol-required tests at a local laboratory. The results and reference ranges of all laboratory tests are to be sent to the Investigator and entered in to the eCRF. ***Note: Investigational product can only be dispensed if central or local laboratory values are available.***
  - Minimum testing required to support the protocol:
    - Liver safety labs: Direct and Total bilirubin; AST, ALT, ALP, GGT, INR, platelet count, sodium, albumin and creatinine.
    - Non-Liver safety labs: CBC & Diff; standard electrolytes (sodium & potassium only), lipid panel, fasting blood glucose, and urine-based β-hCG pregnancy test.
- Investigational Product Distribution: Investigational product may be sent directly to the subject from either the study site or a third-party vendor via a courier service if subjects are not able to attend study site visits. Direct shipment of investigational product from the Investigator site to subjects must adhere to the site's institutional and pharmacy procedures and country specific requirements. If the Investigator is unable to evaluate safety and tolerability and assess the benefit-risk for the individual subject, the subject must interrupt investigational product until the assessment can be completed.

- Home Visits: If laboratory tests cannot be obtained from local laboratories, qualified home nursing support (where available and permitted) is an accepted option that may be employed to supplement telemedicine interactions to enable for the collection and processing of blood samples for laboratory tests including PK and PD samples, if required, and conduct other limited assessments (eg, assessment of vital signs, completion of protocol required subject questionnaires).
- Monitoring: Cancelling or postponing of on-site monitoring visits and extension of the period between monitoring visits may occur per specific local guidelines and regulations. Alternatively, additional off-site monitoring activities such as phone calls, video visits, emails may be used to discuss the trial with the Investigator and site staff. Remote source verification also may be performed if it is permissible by the local regulations.

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

In addition to regularly collected trial data, available COVID-19 related data such as COVID-19 testing will also be collected for all subjects. Any subject that contracts the SARS-CoV-2 virus should have this reported as an adverse event under the description "COVID-19" per MedDRA 23.1. If a subject is hospitalized for COVID-19 complications an SAE should be reported in accordance with the protocol and national requirements.

COVID-19 Vaccine

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

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

11. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

11.1. Investigational Product

Investigational Product will be supplied as white, round, film-coated tablets containing OCA 10 mg, OCA 25 mg, or placebo. All tablets will be debossed with "INT" on one side and "3547" on the other side, and will be of the same size and appearance. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The 25-mg tablet also contains silicon dioxide. The investigational product tablets will be provided in high-density polyethylene bottles with a heat induction seal and child-resistant closures. All investigational product will be manufactured according to Good Manufacturing Practice.

11.2. Investigational Product Packaging and Labeling

11.2.1. Double-Blind Phase

The packaging and labeling of investigational product supplies will be performed according to Good Manufacturing Practice standards by a designated qualified vendor. All investigational product for the Double-Blind Phase will be provided as tablets for oral administration and provided in high-density polyethylene bottles with heat induction seals and child resistant closures, containing 100 tablets. The bottle packaging will not reveal any information about the treatment dose contained in the bottle. Multiple bottles may be dispensed to the subject according to the visit schedule in Table 1 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.

11.2.2. OLE Phase

The packaging and labeling of investigational product supplies will be performed according to Good Manufacturing Practice standards by a designated qualified vendor. All investigational product for the OLE Phase will be provided as tablets for oral administration and provided in high-density polyethylene bottles with heat induction seals and child resistant closures, containing 100 tablets. Multiple bottles may be dispensed to the subject according to the visit schedule in Table 2 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.

11.3. 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.

11.4. Investigational Product Administration

Refer to Section 9.1 and Section 9.2.

11.5. Investigational Product Accountability and Disposal

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

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Investigator or designee will maintain a full record of investigational

product accountability, including records of individual subject dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the Clinical Research Associate (CRA), will review accountability records against investigational product dispensed and that remaining in stock, during on site monitoring visits and when the 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 investigational product for shipment.

12. OVERVIEW OF ASSESSMENTS

Criteria for Evaluation:	
Analyses Variables	**Endpoint Assessments**
Primary Objectives Assessed at the End of the Double-Blind Phase	
Histological improvement in fibrosis using NASH CRN scoring system	Improvement in fibrosis by at least 1 stage with no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase
Secondary Objectives Assessed at the End of the Double-Blind Phase	
Resolution of NASH	No fatty liver disease or fatty liver disease (simple or isolated steatosis) without steatohepatitis AND a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase
	NASH resolution based on pathologist's overall histopathologic interpretation of the presence or absence of definite NASH from Baseline to the end of the Double-Blind Phase
Histological change in fibrosis (improvement and no change)	Change in NASH CRN scoring system from Baseline to the end of the Double-Blind Phase
Clinical outcomes	Occurrence of any of the following adjudicated events: death (all cause); liver transplant; MELD score ≥15; worsening of CP score by at least 2 points; hospitalization (as defined by a stay of ≥24 hours) for variceal bleed, HE (as defined by a West Haven score of ≥2) or SBP (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis); HCC confirmed by 2 complementary imaging modalities unless already confirmed by biopsy

[redacted]

[redacted]

Safety Objectives Assessed at the End of the Double-Blind Phase	
Safety and tolerability	TEAEs, adverse events of special interest (including cardiovascular, pruritus, renal, urinary tracts stones including nephrolithiasis, gallbladder/gallstones-related pancreatitis, hepatic, dyslipidemia and hyperglycemia/new-onset diabetes mellitus AEs), ECGs, vital signs, pruritus VAS, and clinical laboratory assessments (including lipid profile changes)

Criteria for Evaluation:	
Analyses Variables	**Endpoint Assessments**
Markers of cardiovascular safety	Lipoproteins (LDL, HDL, VLDL, ApoB, ApoA-1, ApoE, Lp[a]), total cholesterol, triglycerides, PCSK9, cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, and SCORE)
Adjudicated cardiovascular events for cardiovascular outcomes assessment	Incidence of cardiovascular events including core MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure, and arrhythmias). Other events potentially related to adverse cardiovascular outcomes as defined in Appendix E and included in the CAC charter will be sent to the CAC for adjudication.
Adjudicated events of AKI	Incidence of adjudicated events of AKI
Adjudicated events of hepatic injury	Incidence of adjudicated events of hepatic injury
Primary Objectives Assessed at the End of the OLE	
Analyses Variables	**Assessments**
OLE safety and tolerability	TEAEs, adverse events of special interest (including cardiovascular, pruritus, renal, urinary tracts stones including nephrolithiasis, gallbladder/gallstones-related pancreatitis, hepatic, dyslipidemia and hyperglycemia/new-onset diabetes mellitus AEs), ECGs, vital signs, pruritus VAS, and clinical laboratory assessments (including lipid profile changes)
Clinical outcomes	Occurrence of any of the following adjudicated events: death (all cause); liver transplant; MELD score ≥15; worsening of CP score by at least 2 points; hospitalization (as defined by a stay of ≥24 hours) for variceal bleed, HE (as defined by a West Haven score of ≥2), or SBP (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis); HCC confirmed by 2 complementary imaging modalities unless already confirmed by biopsy

[redacted]

[redacted]

13. EFFICACY ASSESSMENTS

The assessments supporting the efficacy analyses are as follows:

13.1. Liver Biopsies

Given that historical biopsies are to be obtained no more than 12 months before Day 1, slides should be sent for central reading at least 4 weeks before the end of the 12-month window to ensure that the results are available in time for Day 1.

Liver biopsies will generally be obtained from the right lobe of the liver as described in a study-specific histology manual. Liver biopsies should be performed after the hepatobiliary ultrasound for HCC screening. If the initial biopsy was obtained from the left lobe, then subsequent biopsies must be obtained from the left lobe. For subjects who develop potential clinical outcomes or liver-related clinical outcome events during the study, their continued participation in the study is encouraged but biopsies scheduled after the diagnosis based on central reading may not be required.

13.1.1. Central Reading of Liver Histology

Full instructions concerning the number and type of samples to be collected at each visit, the sample collection methods, sample processing, labeling, and shipping will be provided by the Sponsor in a study-specific histology manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

All biopsy assessments will be performed centrally, including assessments of biopsies to determine study eligibility. Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN scoring system must be confirmed for study eligibility. For each biopsy, fibrosis will be graded in accordance with the NASH CRN scoring system (Table 6) (Kleiner 2005).

Table 6: NASH CRN Scoring System for Determining Eligibility and Primary Histological Endpoint Assessment

NAFLD Activity Score (NAS)		**Fibrosis Staging**	
Parameter	Scoring Criteria	Parameter	Staging Criteria
Steatosis	0 = <5% 1 = 5% - 33%	Stage 0	No Fibrosis

NAFLD Activity Score (NAS)		Fibrosis Staging	
	2 = >33% - 66% 3 = >66%		
Lobular Inflammation	0 = No Foci 1 = <2 Foci per 200 × field 2 = 2 - 4 Foci per 200 × field 3 = >4 Foci per 200 × field	Stage 1 Stage 1a Stage 1b Stage 1c	Perisinusoidal or Periportal Mild, zone 3, perisinusoidal Moderate, zone 3, perisinusoidal Portal / periportal

Table 6: NASH CRN Scoring System for Determining Eligibility and Primary Histological Endpoint Assessment (Continued)

NAFLD Activity Score (NAS)		Fibrosis Staging	
Ballooning	0 = None 1 = Few balloon cells 2 = Many cells / prominent ballooning	Stage 2	Perisinusoidal and portal / periportal
		Stage 3	Bridging fibrosis
		Stage 4	Cirrhosis

Biopsy samples will be assessed for quantitative collagen in a subset of subjects as an exploratory objective.

Any extra biopsy tissue may undergo additional histological evaluations such as alpha-smooth muscle actin or bile acid transporter analysis.

13.2. Child-Pugh Assessment

CP score will be calculated as described in Section 7.4.3.1 and according to the frequency listed in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).

13.3. MELD Score

MELD score will be calculated as described in Section 7.4.3.2 and according to the frequency listed in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).

13.4. Prospective Surveillance

HCC screening will include a hepatobiliary ultrasound and AFP assessment according to the schedule presented in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).

For subjects who develop HCC during the study, HCC screening assessments for study visits after onset of HCC are not required.

13.5. Patient-Reported Outcomes and Healthcare Resource Use

Data will be collected to determine the effects of OCA on health-related quality of life. Healthcare resource use as well as a general health status assessment (for the purposes of generating health utilities) will be used to support subsequent cost-effectiveness analyses that are relevant to major health care systems around the world. Assessments of patient-reported outcomes will take place during the visits indicated in Table 1.

The following patient-reported outcomes will be used to evaluate the effects of OCA compared to placebo on improvements in health-related quality of life:

- Chronic Liver Disease Questionnaire (CLDQ-NAFLD): The CLDQ-NAFLD is a modified version of the general CLDQ (Younossi 1999). The CLDQ-NAFLD is a 36-item validated instrument designed to measure health-related quality of life in patients with liver disease (Younossi 2016). The CLDQ-NAFLD is organized into 6 domains: abdominal symptoms, systemic symptoms, fatigue, activity, emotional function, and worry. Each question is answered on a scale from 1 (always) to 7 (never). Therefore, a higher score corresponds to a better quality of life while conversely a lower score corresponds to a worse quality of life.
- EQ-5D-5L: The EQ-5D-5L consists of 2 sections – the descriptive system and the visual analog scales (VASs). The descriptive system is organized into 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the subject's self-rated health on a 20-cm vertical, line with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman 2011, Oemar 2013).
- Work Productivity and Activity Index (WPAI): The WPAI is a validated instrument designed to measure impairment in work and activities. The WPAI is organized into 4 domains: absenteeism, presenteeism, work productivity loss, and activity impairment. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (Prasad 2004).

Subjects will be asked to complete the questionnaires and initial and date each document. The questionnaires should be filed in the subject's study records.

13.6. Noninvasive Assessments of Liver Disease

13.6.1. Noninvasive Scores of Liver Fibrosis

Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI) will be calculated according to the schedule presented in Table 1 (Double-Blind Phase).

13.6.2. Noninvasive Panel of Liver Fibrosis Markers

FibroMeter (Echosens, Paris, France) combines multiple values including Fibroscan TE liver stiffness, age, gender, weight, and blood-based biomarkers (platelets, alpha-2-macroglobulin, ALT, urea, GGT, AST, ferritin, glucose level, and prothrombin ratio) to quantify liver fibrosis. The test can be conducted by staff who are trained in the use and data interpretation of the diagnostic test.

ELF (Siemens Healthcare, Tarrytown, New York, USA) 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.

Noninvasive panel of liver assessments will be performed according to the schedule presented in Table 1 (Double-Blind Phase).

13.6.3. Noninvasive Radiological Liver Fibrosis Measurements

At investigational sites where the device is available, TE using the Fibroscan instrument (Echosens, Paris, France) and MRE, to assess liver fibrosis will be conducted by staff who are trained in the use and data interpretation of the device. Assessments will be performed according to the schedule presented in Table 1 during the Double-Blind Phase only. MRE will be assessed only in subjects enrolled prior to Version 5 of the protocol who had a baseline MRE already performed, not in newly enrolled subjects.

13.7. Efficacy Laboratory Assessments

Refer to Table 13 for a full list of analytes to be tested. Laboratory assessments will be performed according to the schedule presented in Table 1 (Double-Blind Phase) Table 2 (OLE Phase).

HOMA-β and HOMA-IR values will be calculated based on glucose and insulin concentrations.

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

14. CLINICAL PHARMACOLOGY ASSESSMENTS

Subjects who receive at least one dose of OCA and have measurable plasma PK concentration data available will be included in the PK analysis.

A PK blood sample should be collected in subjects who experience an SAE during the study. Blood samples should be collected as soon as possible after the SAE is identified but no later than 7 days after the onset of the SAE. The times of the last dose of investigational product, the last meal, and the PK sample collection should be recorded. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.

14.1. Pharmacokinetic Blood Sampling

Subjects may opt to provide blood samples for serial PK assessments.

Subjects participating in serial PK assessments will provide blood samples for measurement of OCA and its conjugates (glyco-OCA and tauro-OCA) at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post-dose on Month 1, Month 4, Month 12, and Month 18.

Subjects should be reminded to fast for at least 8 hours prior to the PK assessment; although water is allowed during the fasting period. If the subject reports having eaten within the fasting period, this will be documented in the source and the eCRF; however, the PK assessment will still be conducted.

Subjects will then receive a dose of investigational product with approximately 240 mL of water. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be provided following collection of the 1-hour PK sample; the meal will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 6-hour sample collection.

Trough PK blood samples will be obtained at Month 1, 3, 4, 6, 12, and 18 from all subjects.

During the Double-Blind Phase:

- Serial PK samples will be obtained at Month 1, Month 4, Month 12, and Month 18 from subjects who agree to participate in the assessment.
- Trough PK blood samples will be obtained from all subjects prior to dose administration at Months 1, 3, 4, 6, 12, 18, and ET.

For each visit with a PK blood draw, the administration time, date, and timing with respect to food intake of the investigational product, as well as the last dose of investigational product before each visit will be recorded. The collection date and time of each PK blood sample collection will also be recorded. The acceptable windows for the PK sampling time points are listed in Table 7.

Table 7: Acceptable Windows for Pharmacokinetic Sample Collection

Nominal Sampling Time	Acceptable Sampling Window
Before investigational product administration (predose or trough)	Within 30 minutes before dosing
0.5 to 1.5 hours after investigational product dose	±10 minutes
2 to 2.5 hours after investigational product dose	±20 minutes
3 to 6 hours after investigational product dose	±30 minutes

14.2. Processing and Handling of Pharmacokinetic Samples

Whole blood will be collected at each scheduled sample time point. Detailed procedures for the collection of blood samples (including further processing into plasma), storage, and shipment procedures for subsequent bioanalysis will be provided to the investigational site in a separate document before the study is initiated.

14.3. Bioanalysis

Plasma concentrations of OCA and its conjugates (glyco-OCA and tauro-OCA) will be determined using a GLP validated liquid-chromatography-mass spectrometry/ mass spectrometry method. A detailed description of validation information and results from the bioanalytical assay will be provided in separate reports. These samples may be used for evaluation of metabolites of OCA, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by OCA. These data would only be used for exploratory purposes and may not be included in the clinical study report.

Total OCA will be calculated based on OCA, tauro-OCA, and glyco-OCA concentrations.

15. PHARMACODYNAMIC ASSESSMENTS

Pharmacodynamic markers will be collected during the Double-Blind Phase of the study as described in Table 1.

15.1. Markers for FXR Activation

Blood samples will be collected from all subjects to measure 7α-hydroxy-4-cholesten-3-one (C4), fibroblast growth factor-19 (FGF-19), and plasma bile acids as described in Table 1 (Double-Blind Phase).

15.2. Markers of Inflammation, Apoptosis and Necrosis

Blood samples will be collected from all subjects to measure analytes including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF-α), cytokeratin-18 neoepitope M30 (CK-18-M30), and cytokeratin-18 neoepitope M65 (CK-M-65). Assessments will be performed according to the schedules presented in Table 1 (Double-Blind Phase).

15.4. Additional Assessments

[redacted]

16. SAFETY ASSESSMENTS

16.1. Adverse Events and Serious Adverse Events

16.1.1. Definitions of Adverse Events

16.1.1.1. Adverse Event

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

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

Subjects should be questioned in a general way, without leading the subject or asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

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.

16.1.1.2. Treatment-Emergent Adverse Event

A TEAE is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

16.1.1.3. 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 life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen;
- Respite care or observation when there is no AE associated with the hospitalization.

A PK blood sample should be collected in subjects who experience an SAE during the study. Blood samples should be collected as soon as possible after the SAE is identified but no later than 7 days after the onset of the SAE. The times of the last dose of investigational product, the last meal, and the PK sample collection should be recorded. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.

16.1.2. Suspected Unexpected Serious Adverse Reaction

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

SUSARs are subject to expedited reporting. The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening are 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. 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 15 days of first knowledge by the Sponsor. Each competent authority shall ensure that all SUSARs to an investigational medicinal

product that are brought to its attention are recorded. The Sponsor shall also inform all participating Investigators, as applicable to the local regulations.

16.1.3. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 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 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 Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected 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; 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	An event 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.

16.1.4. Relationship to Liver Biopsy

The Investigator will document her/his opinion of the relationship of the AE to liver biopsy using the criteria outlined in Table 9.

Table 9: Relationship of Adverse Events to Liver Biopsy

Relationship	Description
Related	A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the liver biopsy.
Not Related	Any event that does not meet the above criteria.

16.1.5. Relationship to Study Procedures

The Investigator will document her/his opinion of the relationship of the AE to study procedures using the criteria outlined in Table 10.

Table 10: Relationship of Adverse Events to Study Procedures

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

16.1.6. Recording Adverse Event Severity

AEs must be graded for severity (ie, intensity) using the current version of the CTCAE (Appendix D). A severity category of mild, moderate, severe, life threatening, or death as defined in Table 11, must be entered on the AE eCRF.

Because a grading (severity) scale is provided for each AE term and not all grades are appropriate for all AEs, it may be necessary to refer to (Appendix D) before grading the severity of an event.

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. When reporting AEs, reference should be made to the CTCAE manual for guidance on appropriate grading.

Table 11: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
2 = Moderate	Minimal, local or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.[a]
3 = Severe	Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.[b]
4 = Life-threatening	Urgent intervention indicated.
5 = Death	Death related to AE.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

16.1.6.1. Severity of Pruritus (as an Adverse Event)

To ensure consistency in reporting, pruritus AEs must be graded for severity (ie, intensity) using the current version of the CTCAE (Appendix D). As pruritus is a subjective symptom, clinical judgment should be used to determine its severity and management Table 12.

Table 12: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus and Medical Intervention
1 = Mild	Mild or localized; topical intervention indicated.
2 = Moderate	Intense or widespread; intermittent; skin changes from scratching (eg, 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:

- Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the eCRF. Per Section 7.7, subjects with pruritus ≥Grade 3 in severity (per CTCAE) must discontinue investigational product but are encouraged to continue study visits.
- **Short-term use of BAS**
  - Use of BAS may be considered in conjunction with a change in investigational product dosing frequency (ie, every other day dosing) for approximately 2 weeks. The subject should be evaluated after the 2-week intervention to assess the status of pruritus and stop the use of BAS as deemed appropriate by the Investigator. If the Investigator considers that the subject can tolerate investigational product, daily dosing may be reinitiated.
  - If the subject cannot tolerate investigational product after stopping BAS due to ongoing pruritus, the Investigator should consult with the Medical Monitor to determine a treatment plan. This may include continuing every other day dosing, interrupting or discontinuing investigational product.
  - If after 4 to 6 weeks (or up to 3 courses of a 2-week BAS therapy), the subject is unable to tolerate investigational product without BAS treatment, the Investigator should consider, in consultation with the Medical Monitor, discontinuing investigational product.

  - The subject should make every effort to avoid long-term use of BAS for pruritus while taking investigational product. For additional guidance on BAS refer to Section 9.4.3

- Other medical therapies for the management of pruritus may be considered as deemed clinically appropriate and based on current practice guidelines (EASL 2017) or literature (Hegade 2015).
- Less frequent dosing of investigational product (eg, on alternate days) may be tried, after which subjects may return to their original daily dose as soon as tolerated.

16.1.7. Reporting of Adverse Events and Serious Adverse Events

16.1.7.1. 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 of the study.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, 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.

Redacted medical record source documentation will be requested for all SAEs.

16.1.7.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor. Immediate reporting implies within 24 hours of becoming aware of the occurrence of an SAE.

All SAEs (including potential liver-related clinical outcome events that qualify as serious) must be reported to the Sponsor. SAEs are reported by entering the SAE data into the study specific electronic data capture (EDC) system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may reported by:

If an SAE is reported by telephone or fax, an SAE Report form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Subject number
- Event term
- At least 1 criterion classifying the event as serious

- Name and title of the reporting individual
- Causal relationship to the investigational product

The Investigator will assess whether the event is causally related to the investigational product. The Sponsor will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators of investigational new drug (IND) Safety Reports/Expedited Safety Reports that occur during the 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 [redacted] s soon as possible.

The Investigator is responsible for submitting information on IND Safety Reports/Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local-country requirements.

Documentation of the submissions to IECs/IRBs must be retained in the appropriate study file(s). As instructed by the Sponsor, IND Safety Reports/Expedited Safety Reports should be retained in the appropriate investigative site study files, or with the IB.

16.1.8. Potential Liver-Related Clinical Outcome Events

Specified liver-related clinical outcome events may, by definition, qualify as SAEs (see Section 16.1.1.3). The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section 16.1.7.2). The Sponsor is responsible for regulatory reporting of SAEs, including expeditious reporting of SUSARs, refer to Section 16.1.2 for definition of SUSAR.

16.1.9. 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 with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the Medical Monitor.

16.1.10. 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 16.1.7.2.

16.1.11. 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 16.1.7.

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 (ie, within 24 hours) by following the instructions provided in Section 16.1.7.

16.1.12. 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. If resolved, a resolution date for the AE should be documented on the eCRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

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

If a subject experiences symptoms consistent with symptomatic cholelithiasis and/or complications related to gallstone disease or pancreatitis, the subject should have investigational product interrupted while undergoing a complete evaluation for both conditions consistent with local standards of care. If symptomatic cholelithiasis and/or cholecystitis is diagnosed, the subject should be managed and monitored as described in Section 7.5.1.

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 local standard of care. If treatment-emergent acute, or nonacute pancreatitis is diagnosed, investigational product must be discontinued, and the subject should be managed and monitored as described in Section 7.5.2. The Investigator should contact the Medical Monitor upon awareness of pancreatitis. Results should be recorded promptly in the eCRF.

16.1.13. 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 interrupt treatment with investigational product immediately (Section 8.2.1.4) 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 downloading and completing the Pregnancy Report Form. Any rechallenge of the investigational product should be implemented per the criteria outlined in Table 5.

The pregnancy Report Form must be emailed to sae@interceptpharma.com or faxed to 1-800-497-8521.

In the situation that the EDC is not functioning, the Medical Monitor should be notified by telephone. The investigator remains responsible for entering the pregnancy information into the EDC when the EDC becomes functional.

The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor. The investigator should notify the Sponsor of the outcome of the pregnancy by completing Pregnancy Follow-up section in the EDC. In the situation that the EDC is no longer available due to study closure, the outcome of the pregnancy should be added to the pregnancy resolution section of the downloaded Pregnancy Outcome Form and faxed or emailed to the Sponsor. Thereafter, the subject and infant must be followed as considered appropriate by the Investigator and any new updates should be sent to the Sponsor.

Completing the pregnancy report form in the EDC 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 16.1.7 must also be followed.

16.2. Other Safety Parameters

16.2.1. Medical History/Demographics

A complete medical history will be obtained from the subject at Screening. Smoking and alcohol consumption history and current habits will be recorded. Demographic characteristics (age, sex, race, and ethnicity) will be recorded. Baseline pruritus by severity will be obtained on Day 1 using the Pruritus VAS questionnaire.

16.2.2. 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 1 (Double-Blind Phase) and Table 2 (OLE Phase). A basic physical examination should be performed, including all body systems pertinent to the subject. Any clinically significant abnormality should be reported on the AE eCRF page.

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

16.2.3. Vital Signs

Vital signs will be assessed at the visits as specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase): temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes. 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.

16.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected as specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).

All ECGs should be performed before blood draws. 12-lead ECG results will be reviewed by the Investigator or designee and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE eCRF page.

Investigative sites must retain a copy of all 12-lead ECGs. These ECGs must be clearly labeled with the Subject ID number, date, and time. Full instructions will be provided for forwarding the 12-lead ECGs for central reading.

16.2.5. Alcohol Consumption, Smoking Habits, and Caffeine Consumption

Information about the subject's alcohol consumption, smoking habits, and caffeine consumption will be collected during the visits indicated in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase) using the AUDIT, smoking habits, and caffeine consumption eCRFs. AUDIT is a 10-item questionnaire that uses the domains of alcohol consumption, drinking behavior, and alcohol-related problems (Saunders 1993).

16.2.6. Cardiovascular Risk Scores

Cardiovascular risk scores (10-year ASCVD Risk, FRS, Reynolds score, and SCORE) will be calculated according to Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).

16.2.7. Laboratory Assessments

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

Blood and urine samples for laboratory assessments will be collected at the visits specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase). 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 a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit.

If 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 laboratory is required. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges. All local laboratory data, including the reference ranges, are to be collected and entered in the eCRF within 2 days of receiving the results. For guidance on alternative processes under which subjects may complete the protocol-specified assessments under COVID-19 restrictions refer to Section 10.

All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.

The Investigator should proactively monitor and manage lipid levels in all subjects as indicated via appropriate medical interventions (eg, statins). Recent guidelines stress the importance of evaluating ASCVD risk in all subjects to help guide decisions in recommending therapies and reducing LDLc to reduce the risk and prevent onset or recurrence of ASCVD (refer to Section 9.4.5 and Appendix A.

Urine based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol specified visits (Table 1) [Double-Blind Phase] and Table 2 [OLE Phase]). If a urine pregnancy test is positive, a serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified and the subject will be followed as outlined in Section 16.1.13 until pregnancy outcome.

An assessment of steady-state exposures (on an aggregate level) will be performed by an internal Intercept clinical pharmacologist/pharmacometrician or designee who is discrete from the study team. These results may be made available to the DMC as appropriate (see Section 17.13).

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

Table 13: List of Laboratory Scores and Analytes

Laboratory Assessment (Phase)	Scores and Analytes[a]
Serum chemistry (Double-Blind and OLE)	Albumin, BUN, creatinine, conjugated (direct) bilirubin, total bilirubin, AST, ALT, ALP, GGT, electrolytes (calcium, chloride, magnesium, phosphorus, potassium, sodium), total protein, bicarbonate, free fatty acids, creatine phosphokinase, LDL, HDL, VLDL, total cholesterol, triglycerides, and calculation of eGFR
Hematology (Double-Blind and OLE)	Hemoglobin, hematocrit, white blood count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets, and red blood cell count (including MCV, MCH, MCHC)
Urinalysis (Double-Blind and OLE)	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, microscopic exam, creatinine, albumin, leukocytes, nitrates, and albumin/creatinine ratio
Coagulation (Double-Blind and OLE)	PT, aPTT, INR
Metabolic parameters (Double-Blind and OLE)	Fasting plasma glucose, insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR
Noninvasive scores of liver fibrosis (Double-Blind and OLE)	NFS, FIB-4, and APRI
Noninvasive panel of liver fibrosis (Double-Blind and OLE)	ELF: HA, P3NP, TIMP-1 Fibrometer: platelets, alpha-2-macroglobulin, ALT, urea, GGT, AST, ferritin, glucose level, and prothrombin ratio
Lipoprotein analysis (Double-Blind and OLE)	ApoA-1, ApoB, ApoE, Lp(a), and PCSK9
Markers of inflammation, apoptosis, necrosis (Double-Blind)	hs-CRP, IL-6, and TNF-α, CK-18-M30, and CK-M65
Thyroid function tests (Double-Blind and OLE)	Free T3, free T4, and TSH
HCC screening (Double-Blind and OLE)	AFP
Virology (Double-Blind)	HBsAg, HCV
Pregnancy test (female subjects of childbearing potential) (Double-Blind and OLE)	β-hCG
PD assessment (Double-Blind)	C4 and FGF-19, and plasma bile acids
PK analytes (Trough PK) (Double-Blind)	OCA, tauro-OCA and glyco-OCA and possible other analytes not yet identified
Exploratory biomarkers of disease severity (Double-Blind)	CHI3L1, and emerging biomarkers for NASH diagnosis and/or pathophysiology
Cardiovascular risk scores	10-year ASCVD Risk, FRS, Reynolds score, and SCORE
HepQuant-SHUNT tests (Double-Blind)	d4-cholate, 13C-cholate
Optional Assessments	
Laboratory Assessment (Phase)	**Analyte**
PK analytes (Serial PK; Double-Blind)	OCA, tauro-OCA and glyco-OCA and possible other conjugates or metabolites not yet identified

AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoA-1 = apolipoprotein A-1; ApoB = apolipoprotein B; ApoE = apolipoprotein E; APRI = aspartate aminotransferase to platelet ratio index; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; aPTT = partial thromboplastin time; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; C4 = 7α-hydroxy-4-cholesten-3-one; CHI3L1= chitinase 3-like protein 1; CK-18-M30 = cytokeratin-18 neoepitope M30; CK-18-M65 = cytokeratin-18 neoepitope M65; eGFR = estimated glomerular filtration rate; ELF = Enhanced Liver Fibrosis; FIB-4 = Fibrosis-4; GGT = gamma-glutamyl transferase; FGF-19 = fibroblast growth factor 19; FRS = Framingham Risk Score; glyco-OCA = glycine conjugate of obeticholic acid; HA = hyaluronic acid; HbA1c = hemoglobin-specific A1c fraction; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HDL = high-density lipoprotein; HOMA-β = homeostatic model assessment – beta cell; HOMA-IR = homeostatic model assessment – insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; INR = international normalized ratio; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NASH = nonalcoholic steatohepatitis; NFS = NAFLD fibrosis score; OCA = obeticholic acid; OLE = open-label extension; PD = pharmacodynamics; PCSK9 = proprotein convertase subtilisin/kexin type 9; P3NP = procollagen III amino terminal peptide; PK = pharmacokinetic; PT = prothrombin time; SCORE = systemic coronary risk evaluation; T3 = triiodothyronine; T4 = thyroxine; tauro-OCA = taurine conjugate of obeticholic acid; TIMP-1 = tissue inhibitor of metalloproteinase 1; TNF-α = tumor necrosis factor-α; TSH = thyroid-stimulating hormone; US = United States; VLDL = very low-density lipoprotein

[a] Overlapping analytes will be analyzed only once.

16.2.8. Pruritus Assessment

Pruritus Visual Analog Scale (VAS): The pruritus VAS will be used to assess a subject's experience and severity of pruritus. This assessment should be captured on the blue pad.

17. STATISTICS

A detailed statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests, will be prepared and approved by the Sponsor and its designees. A separate clinical pharmacology analysis plan will be prepared, providing details of PK analysis methods and parameter estimation. PK/PD analytical methods will be detailed in a separate modeling and simulations plan, and all results will be documented separate from the clinical study report. Details about these specific planned analyses will be prepared and approved by the Sponsor or its designees prior to study database lock.

17.1. Analysis Populations

- Intent-to-Treat (ITT) Population will include all randomized subjects. The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.
- Modified ITT Population (mITT) will include all ITT subjects except those who are not eligible to dose titrate due to safety or tolerability reasons. Treatment assignment will be based on the randomized treatment.
- The Per Protocol (PP) Population will include all mITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusions. Treatment assignment will be based on the randomized treatment.
- The Safety Population will include all randomized subjects who receive at least 1 dose of investigational product (OCA or placebo). The Safety Population will be

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

- The PK Population will consist of all subjects who receive OCA, have at least one confirmed analyzable sample, and have no major protocol deviations that may potentially affect the PK analysis. The final determination of subjects included in the PK Population and the samples included in the analysis will be determined based on a review of data before database lock. The PK population will be the population used for OCA PK and PK/PD analyses.

Additional analysis population (if any) will be specified in the SAP.

17.2. Determination of Sample Size

A sample size of 300 subjects per group will provide at least 90% power to detect a statistically significant treatment difference of 10% between OCA 25 mg and placebo groups based on a Chi-square test with 2-sided type I error at 0.05 level, assuming a responder rate of 10% in the placebo group. As there was no previous study performed using the same endpoint in this disease, the assumption was determined based on data from literature, and results from the FLINT study and Study 747-303.

17.3. Primary Efficacy Analysis

The primary efficacy analysis will be conducted using the ITT population and test the following hypotheses:

- H_{01}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is equal between placebo and OCA 10 to 25 mg titration.
- H_{11}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is different between placebo and OCA 10 to 25 mg titration.
- H_{02}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is equal between placebo and OCA 10 mg.
- H_{12}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to the end of the Double-Blind Phase is different between placebo and OCA 10 mg.

The overall type I error for primary efficacy analysis will be controlled at 0.05. The primary analysis between placebo and OCA 10 to 25 mg titration will be tested first at 5% alpha and the hypothesis (H_{02}) between placebo and OCA 10 mg will be tested if the null hypothesis (H_{01}) between placebo and OCA 10 to 25 mg titration is rejected at 5% level.

For the comparison of the primary efficacy endpoint, a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] will be performed. Additional details regarding analyses with missing values will be provided in the SAP.

Analyses of the primary endpoint will be conducted using the mITT and PP populations and a sensitivity analysis will be conducted in the Month 18 biopsy-only population.

17.4. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted using mITT and PP populations.

17.4.1. Histology Endpoints

The following secondary efficacy endpoints will be analyzed:

- Percentage of subjects with resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" as characterized/quantified by a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, at the end of the Double-Blind Phase
- Percentage of subjects with resolution of NASH based on pathologist's overall histopathologic interpretation of the presence or absence of definite NASH at the end of the Double-Blind Phase
- Histological changes in fibrosis status including: (1) improvement, or (2) no change, from Baseline to the end of the Double-Blind Phase using the NASH CRN scoring system

Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no]).

Overall shift and frequency tables will be presented for NAS components and fibrosis scores (according to NASH CRN criteria).

17.4.2. Clinical Outcomes

Analyses of the clinical outcomes composite endpoint and occurrence of HCC will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo. Treatment groups will be compared on the percentage of subjects who reported any of the following adjudicated events, as well as the time to first occurrence:

- Death (all cause)
- MELD score ≥15
- Liver transplant
- Worsening of CP score by at least 2 points
- Hospitalization (as defined by a stay of ≥24 hours) for onset of:
    - Variceal bleed

  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)
- HCC (as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy) will be analyzed as a separate outcome event.

Only adjudicated events will be included in analyses. Subjects with none of these events will be censored at the date of last contact. For the analysis of time to first occurrence of adjudicated events, a log rank test stratified by the randomization stratification factor (presence of type 2 diabetes at enrollment [yes/no]) will be used. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians and corresponding 95% confidence intervals (CIs), if the medians can be estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. Subjects without any documentation of events will be censored at the date of last contact by the end of the Double-Blind Phase.

In addition, treatment groups will be compared on each component of the outcome events.

The percentage of subjects who reported any adjudicated events will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no]). Percentage of subjects who reported each component of the outcome events will also be analyzed separately in a similar manner.

[redacted]

[redacted]

17.9. Handling of Missing Data

Subjects who discontinue investigational product are expected to continue in the study until study termination.

In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

17.9.1. Time-to-Event Endpoints

For the time-to-event analyses, subjects who do not experience an event will be censored at the time of their last contact.

All time-to-event endpoints include only adjudicated events. Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

17.9.2. Quantitative Endpoints

For exploratory efficacy endpoints utilizing an ANCOVA model or the Wilcoxon Rank Sum Test, observed cases will serve as the primary analysis. Sensitivity analyses to assess the effect of missing data may be conducted where missing data is imputed using last observation carried forward. The last on-treatment value, scheduled or unscheduled, will be carried forward to the missing timepoint.

Sensitivity analyses of ANCOVA models for exploratory efficacy endpoints will also be evaluated using a restricted maximum likelihood based mixed-effect repeated measures model where no imputations will be made for missing values.

17.9.3. Responder Endpoints

For the primary analyses, in which subjects are classified as either a responder or a non-responder (binary outcome), any subject who does not provide an assessment at the specified timepoint for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator. Additional details regarding the secondary histological endpoints are provided in the SAP.

An "observed cases" analyses will also be conducted as sensitivity analyses, excluding those subjects who do not provide an assessment at the specified timepoint for the defining of response. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

17.9.4. Incidence Endpoints

For the analyses of the percentage of subjects who reported any of the adjudicated clinical outcome events or adjudicated cardiovascular events, all subjects, regardless of whether one has reported any adjudicated events will be included in the denominator, and only subjects with adjudicated events will contribute to the numerator. This represents the proportion of subjects experiencing events to number of subjects at risk.

Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.

17.11. Safety Analyses

Safety evaluations will comprise treatment-emergent AEs, AEs of special interest (including cardiovascular, pruritus, renal, urinary tracts stones including nephrolithiasis, gallbladder/gallstone-related, pancreatitis, hepatic, dyslipidemia and hyperglycemia/new-onset diabetes mellitus AEs), adjudicated CV events, adjudicated AKI events, adjudicated events of hepatic injury, vital signs, electrocardiograms (ECGs), pruritus VAS, and clinical laboratory results.

Safety data will be summarized by treatment group using the Safety Population.

17.11.1. Adverse Events

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

Adverse events of special interest, to be specified in the SAP, will be summarized for each treatment group.

17.11.2. Hepatic and Renal Safety Adjudication

Potential events of hepatic injury and AKI will be adjudicated during the study (Section 17.14). The adjudication of the events of hepatic injury will be separate from the adjudication of events for the assessment of outcomes in this study. The adjudication of potential events of hepatic injury and AKI will be further defined in the HSAC charter and the Renal Adjudication Committee charter, respectively.

17.11.3. Cardiovascular Event Adjudication

Specific details of the events that will be adjudicated by the Cardiovascular Adjudication Committee 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.

Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure and arrhythmias). Any hospitalization (≥24 hours) where a cause has not been identified by the Investigator will be considered as a cardiovascular event and sent for adjudication. Other events potentially related to adverse cardiovascular outcomes are defined in Appendix E and will be included in the Cardiovascular Adjudication Committee Charter for adjudication.

Summaries of adjudicated cardiovascular events will include the incidence of TEAEs, the incidence of serious TEAEs, and a time-to-event analysis as described below. All summaries of incidence will include the associated exact binomial 95% CI.

The time-to-event endpoints include:

- Time from randomization to the first confirmed occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or nonfatal unstable angina requiring hospitalization
- Time from randomization to the confirmed occurrence of cardiovascular death (including fatal myocardial infarction, fatal stroke)
- Time from randomization to the first confirmed occurrence of myocardial infarction (nonfatal or fatal)
- Time from randomization to the first confirmed occurrence of stroke (nonfatal or fatal)
- Time from randomization to the confirmed occurrence of death from any cause
- Time from randomization to the first confirmed occurrence of unstable angina requiring hospitalization (nonfatal or fatal)
- Time from randomization to the first occurrence of coronary revascularization procedure
- Time from randomization to the first occurrence of hospitalization for congestive heart failure
- Time from randomization to the first occurrence of transient ischemic attack
- Time from randomization to the first occurrence of arrhythmia

Placebo and OCA will be compared separately using a log rank test stratified by the randomization stratification factor. KM estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. Subjects without any documentation of events will be censored at the date of last contact. The tabulation will include the KM estimate of the medians and corresponding 95% CIs, if the medians can be estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

17.11.4. Cardiovascular Risk Assessment

The following cardiovascular risk assessments will be calculated:

- 10-year ASCVD Risk based on Pooled Cohorts Equation
- FRS
- Reynolds score
- SCORE

Each score is derived from a subject's age, sex, smoking status, total cholesterol, HDL, and LDL levels, systolic blood pressure, diastolic blood pressure, and other factors including family history, BMI, ethnicity, and medications.

These cardiovascular assessments will be summarized by treatment group using descriptive statistics at Baseline and at Month 12 and 18 Visits. The change and percentage change from Baseline and the changes from baseline in risk categories based on these scores will also be summarized. Baseline is defined as the last assessment before treatment.

17.11.5. Clinical Laboratory Evaluations

Central laboratory parameters will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations before treatment.

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

17.11.5.1. Lipoprotein Evaluations

Lipoprotein samples will be obtained, assayed, and analyzed. The lipoprotein analyte values, change from baseline, and percentage change from baseline will be summarized by treatment group for the lipoprotein analytes. Baseline is defined as the last fasting assessment before treatment. This analysis will use only samples that have a confirmed fasting of approximately 8 hours or more before their visit. Further analyses of lipoprotein analytes will be specified in the SAP.

Subgroup analyses will also be presented by use of statin medication.

17.11.6. Additional Safety Analyses

17.11.6.1. Vital Signs

The results and change from baseline to each on-study evaluation visit will be summarized for body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes.

17.11.6.2. Electrocardiograms

The ECG data analysis will be conducted based on methodology recommended in the International Conference on Harmonisation (ICH) E14 guideline, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs.

Baseline is defined as the mean of all available evaluations prior to treatment. Descriptive statistics of ECG parameters (time between 2 consecutive R waves [RR], PR, QRS, QT, and QT interval corrected by Fridericia's formula [QTcF]) at baseline and at each post-baseline timepoint will be summarized by treatment group; absolute changes from baseline will also be summarized.

A categorical summary of abnormal QTcF values will be presented by treatment group. The number of patients with values of >450 msec, >480 msec, and >500 msec will be presented, and the number of patients with change from baseline values of >30 msec and >60 msec will also be presented.

Overall interpretation results for ECGs and the investigator interpretation results are collected as normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS). Subjects whose interpretation shifts from normal to abnormal (CS or NCS) will be listed separately including description of the abnormality and any associated comments.

17.11.6.3. Pruritus VAS

The pruritus VAS will be used to assess a subject's experience and severity of pruritus and will be analyzed as described in Section 16.2.8.

17.12. Open-Label Extension Analyses

17.12.1. Safety Analyses (OLE)

Safety evaluations conducted during the Double-Blind Phase will also be conducted for the OLE. For quantitative parameters including, but not limited to, vital signs, ECG, and clinical laboratory results, changes from double-blind baseline value and OLE baseline value will be presented. Analyses based on the double-blind baseline will be performed using the treatment actually received in the Double-Blind Phase. Analyses based on the OLE baseline will be based on the treatment actually received in the OLE Phase.

17.12.2. Efficacy Analyses (OLE)

The occurrence of all-cause mortality and liver-related clinical outcomes (refer to Section 17.4.2) will be summarized. For additional exploratory analyses, please refer to SAP for more details.

17.13. Data Monitoring Committee

An independent data monitoring committee (DMC) will include hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), DILI expert(s), and statistician(s); they will not be involved in the study as Investigators, adjudication committee members, or consultants. The DMC will have oversight over the study conduct as defined by the DMC charter. All members will have considerable experience with clinical study conduct and DMCs. Any candidate found to have a conflict of interest or whose name is listed on the FDA debarment list will not be offered membership. 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 review the safety data, which will include AE data as well as lab values. PK results will be made available to the DMC as appropriate.

The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review PK, safety and efficacy data as well as the adjudication assessments from the 4 adjudication committees listed in Section 17.14. 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. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked.

Summary tables reviewed by the DMC during closed sessions will be unblinded and include an overall column containing information regarding all subjects and separate treatment columns with fake labels, ie, the actual treatment groups are used but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA-coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs. In addition, specific summary data focused on hepatic and renal safety are reviewed by the DMC, including an aggregate unblinded summary of adjudicated cases of suspected hepatic injury and AKI, provided on a quarterly basis or ad hoc as appropriate.

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.

17.14. Adjudication Committees

Potential liver-related clinical outcomes and potential events of hepatic injury, AKI, MACE, deaths, and hospitalizations (depending on the cause) that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The 4 committees and event types they are responsible for adjudicating are as follows:

- Cardiovascular Adjudication Committee: Adjudicates all potential MACE, (including all deaths) and hospitalizations (depending on the cause)
- Hepatic Outcomes Committee: Adjudicates all deaths and potential liver-related clinical outcomes
- HSAC: Adjudicates all events of potential hepatic injury
- Renal Adjudication Committee: Adjudicates all potential events of AKI

Each adjudication committee will have 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.

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. Specific details of the events that will be adjudicated by the Cardiovascular Adjudication Committee, Hepatic Outcomes Committee, HSAC, and the Renal Adjudication Committee 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 Any candidate found to have a conflict or whose name is listed on the FDA

debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest, they will be replaced.

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

18. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

The Investigator may exercise judgment in allowing the CRA access to particular sections of the subject's medical records if these are deemed irrelevant to the performance, observations, or conduct of this study.

18.2. 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 be available for discussion about the study.

19. 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 (eg, 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 18.2 for more details regarding the audit process.

20. ETHICS

20.1. 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 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 prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. The Sponsor will provide this information to the Investigator.

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

20.2. 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.

20.3. Written Informed Consent

The Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible 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.

20.4. 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 (eg, CRA, Medical Monitor), auditors, and inspectors will require access to a subject's medical notes for the purpose of source document verification, but the subject's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The 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 (eg, subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

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

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

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

21. INVESTIGATOR OBLIGATIONS

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

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

21.1. 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 (Section 16.1.7).

21.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in 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. The only exception is when the Investigator considers a subject's safety to be compromised if immediate action is not taken.

21.3. 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 (US only); in lieu of 1572 (for ex-US)
- Current medical license of Investigators
- Curriculum vitae of Investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

21.4. Ethics Review (IRB/IEC)

Please see Section 20.1 for the Investigator's responsibilities regarding ethics review.

21.5. 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.

22. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

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

- Clinical Trial Registries (eg, www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (eg, 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.
- Data Management: The Sponsor will establish data management plan and SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions prior to the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data prior to the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.
- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.
- Single Center Publication and Additional Publications: This is a multicenter 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 prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of 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, eg, protocol and amendments, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

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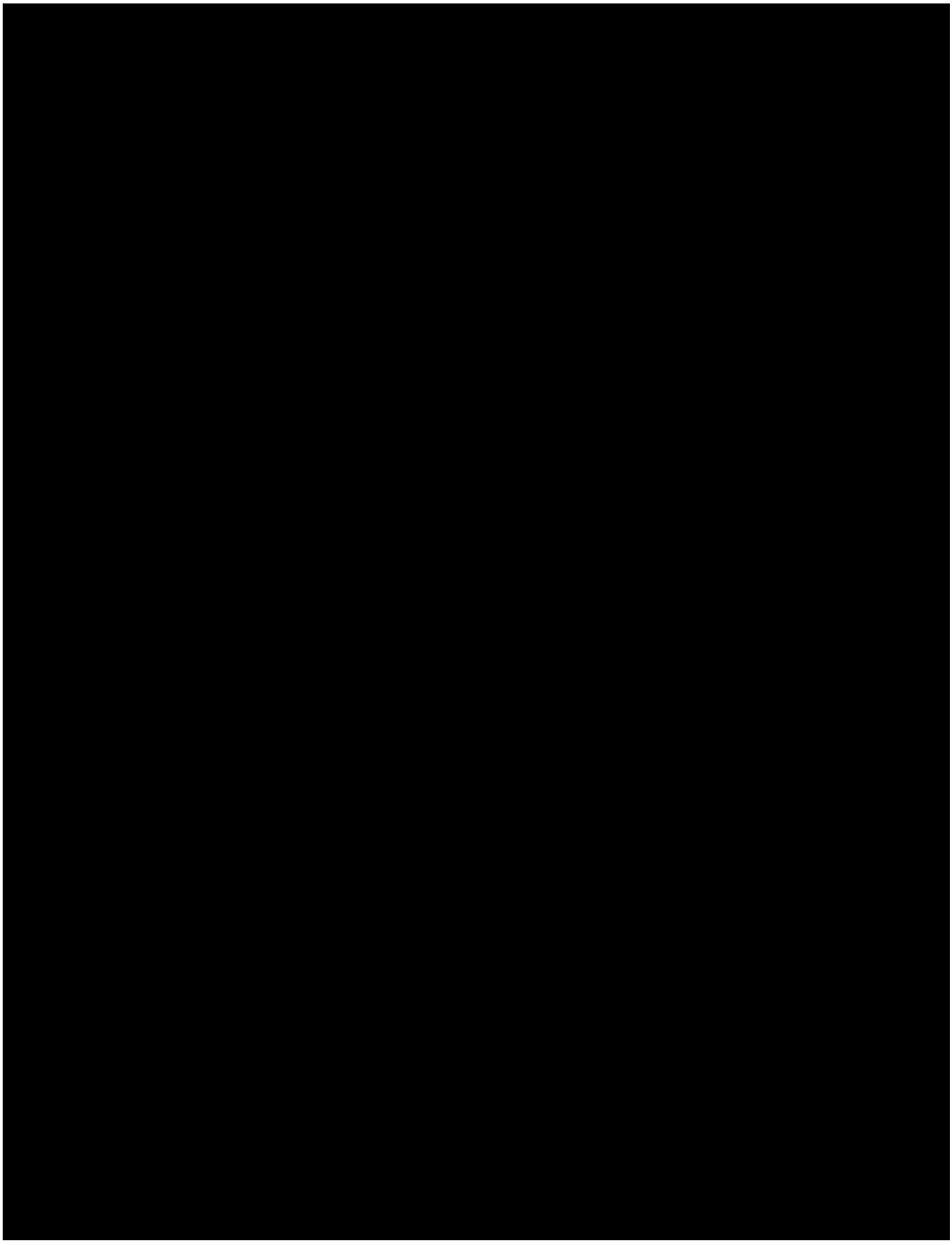

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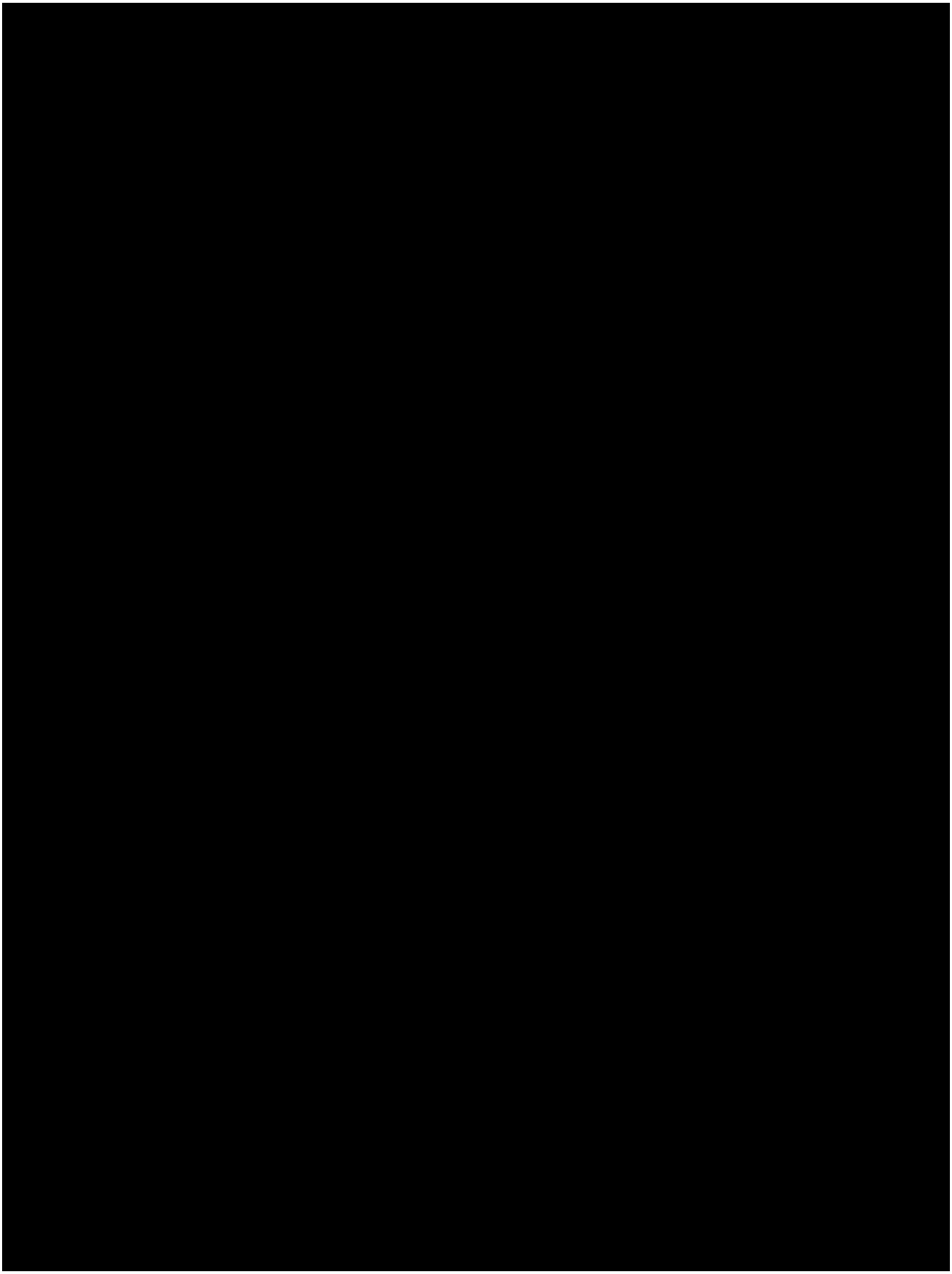
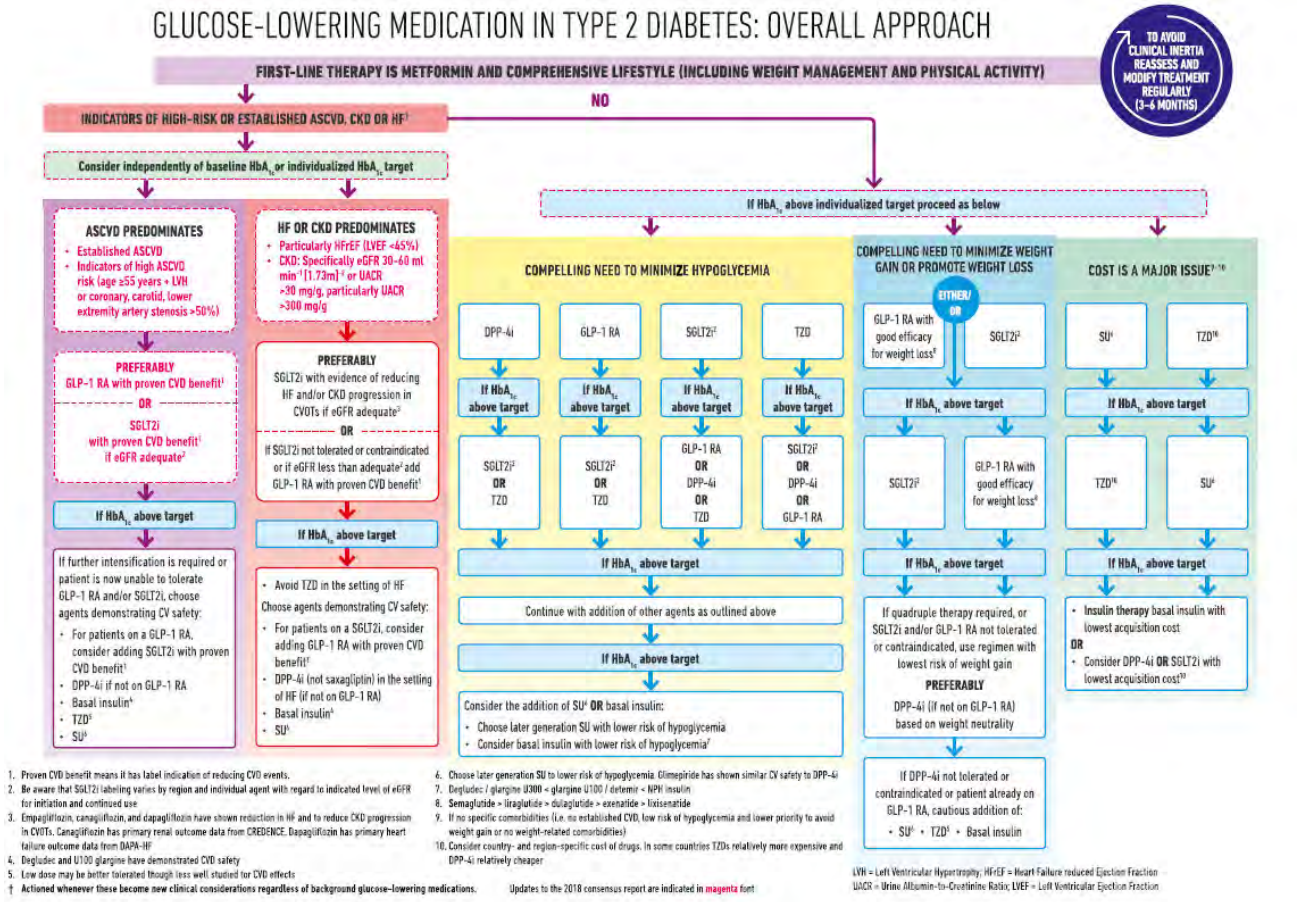


APPENDIX B. MANAGMENT OF HYPERGLYCEMIA

The selection of the appropriate individualized therapy is described in current guidelines to assess risk of hyperglycemia (Figure B1; Buse 2020)

Figure B1: Glucose-Lowering Medication in Type 2 Diabetes: Overall Approach



RA = receptor agonist; SU = sulfonylureas; TZD = thiazolidinediones.
Source: Buse 2020.

APPENDIX C. EDUCATION AND ASSESSMENT OF SIGNS/SYMPTOMS OF INTERCURRENT ILLNESS AND/OR POTENTIAL ADVERSE EVENTS AT EACH STUDY VISIT

Subjects should be educated to understand and recognize the signs and symptoms of intercurrent illnesses and/or potential adverse events listed below. Investigators should instruct subjects to seek immediate medical attention if they experience any of these signs or symptoms.

At each visit, study site staff should inquire if the subject has developed any of the listed signs and symptoms; received any new drug prescriptions, any new over the counter medications, or herbal supplements from health care providers (HCPs); or had any laboratory procedures or assessments performed by an HCP.

Events	Signs and Symptoms
Cholelithiasis **(Protocol Section 7.5.1)**	• Upper abdominal pain or tenderness (particularly post-prandial), abdominal swelling, nausea, vomiting, or fever
Acute cholecystitis, or Acute pancreatitis **(Protocol Section 7.5.2)**	• Symptoms of these events may be similar to symptomatic cholelithiasis (see Protocol Section 7.5.1) • Significant upper abdominal pain with nausea, vomiting, fever, or jaundice
Hyperglycemia **(Protocol Section 9.4.6)**	• Polyuria, polydipsia, polyphagia, blurred vision, fatigue, and headaches
Renal Impairment **(Protocol Section 7.6.1)**	• New onset fatigue/asthenia, nausea, or confusion and to assess signs such as decreased skin turgor (dehydration), increased heart rate, lower extremity edema, decreased urine output or dark urine
Nephrolithiasis **(Protocol Section 7.6.2)**	• Evidence of hematuria, flank or lower abdominal pain, nausea, vomiting, fever, or chills
Hepatic Injury and/or decompensation **(Protocol Section 7.4)** **Questions to ask subjects are listed below**	• Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark], severe fatigue, right upper quadrant pain, rash, eosinophilia • More general signs and symptoms of ascites and encephalopathy: swelling of the legs or abdomen, confusion or abrupt abnormal behavior • Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite

	• Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea) and should be an indication for prompt investigational product interruption and complete subject evaluation **Other Symptoms:** • Worsening or new pruritus • Decreased urine output, dizziness, or lethargy

Follow up Questions for Positive Response to Signs/Symptoms of Hepatic Injury or Decompensation

1. Example 1: If subject is experiencing abdominal pain, follow-up questions may include:
    a. For how long?
    b. What is the location?
    c. Is it constant?
    d. What makes it better? Worse? (eg, eating, movement)
    e. Have you ever felt pain or similar discomfort before?
    f. Is it associated with nausea or vomiting or diarrhea?
    g. Are you having fevers?
2. Example 2: If subject is experiencing itching, follow up questions may include:
    a. Is this new?
    b. If so, how severe is it?
    c. Is it limiting your daily activities?
    d. Is it limiting your sleep?
    e. Is it constant?
    f. Do you have a rash? Where is it located?
    g. Arms/legs/chest/entire torso/back/face?
3. Example 3: If subject is experiencing nausea, vomiting, and/or diarrhea, follow-up questions may include:
    a. If so, for how long?
    b. Which of the three symptoms do you have?
    c. Are they associated with fever? With chills? With yellowing of your eyes? With rash?
    d. Is anyone close to you having similar symptoms?
4. Example 4: If subject has noticed that their stool is now pale-colored or urine is darker than usual, follow-up question may include:
    a. If so, for how long?
    b. Is your urine darker than usual?
    c. Are the whites of your eyes yellow?
    d. Is your skin yellow?
5. Example 5: If subject has noticed feeling dehydrated or is not urinating as often as usual, follow up question may include:

a. Are you excessively thirsty?
b. Are you feeling dizzy or lethargic and weak?

APPENDIX D. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

APPENDIX E. STANDARDIZED DEFINITIONS FOR CARDIOVASCULAR ENDPOINT EVENTS

Event	Definitions
Cardiovascular (CV) Death:	
Death due to Acute MI	Death due to Acute MI refers to a death by any CV mechanism (eg, arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days[a] after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days of the MI, it will be considered a death due to MI. Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (Clinical Data Interchange Standards Consortium [CDISC], Chapter 4) or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery [CABG]), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (ie, chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.
Sudden Cardiac Death	Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths: c. Death witnessed and occurring without new or worsening symptoms d. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI e. Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review) f. Death after unsuccessful resuscitation from cardiac arrest (eg, implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest) g. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology h. Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death (information regarding the subject's clinical status preceding death should be provided, if available). Unless additional information suggests an alternate specific cause of death (eg, death due to Other CV Causes), if a subject is seen alive ≤24 hours of being found dead, sudden cardiac death (criterion f above) should be recorded. For subjects who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (eg, a subject found dead in bed, but who had not been seen by family for several days).

Event	Definitions
Death due to HF	Death due to HF refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology (CDISC, Chapter 7). Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
Death due to Stroke	Death due to Stroke refers to death after a stroke (hemorrhagic, ischemic, or undetermined) that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (CDISC, Chapter 6).
Death due to CV Procedures	Death due to CV Procedures refers to death caused by the immediate complications of a cardiac procedure.
Death due to CV Hemorrhage	Death due to CV Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (CDISC, Chapter 6), non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage causing cardiac tamponade.
Death due to Other CV Causes	Death due to Other CV Causes refers to a CV death not included in the above categories but with a specific, known cause (eg, pulmonary embolism or peripheral arterial disease).
Non-CV Death:	
The following is a suggested list of non-CV causes of death: • Pulmonary • Renal • Gastrointestinal • Hepatobiliary • Pancreatic • Infection (includes sepsis) • Inflammatory (eg, Systemic Inflammatory Response Syndrome (SIRS) / immune (including autoimmune; may include anaphylaxis from environmental [eg, food] allergies) • Hemorrhage that is neither CV bleeding nor a stroke (see	Non-CV death is defined as any death with a specific cause that is not thought to be CV in nature, as listed in CDISC Chapter 1, or as listed for CV Death.

Event	Definitions
Chapter 1, Section 6, and Chapter 6) • Non-CV procedure or surgery • Trauma • Suicide • Non-prescription drug reaction or overdose • Prescription drug reaction or overdose (may include anaphylaxis) • Neurological (non-CV) • Malignancy • Other non-CV	
Undetermined Cause of Death:	
Undetermined Cause of Death (will be classified as a CV death)	Undetermined cause of death refers to a death not attributable to one of the above categories of CV death or is due to a non-CV cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is "subject died") or there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few subjects in well-run clinical trials.
Cardiovascular Events:	
Myocardial Infarction[b]	a) Clinical Presentation The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (eg, trauma, surgery, pacing, ablation, HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process. b) Biomarker Elevations For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the ninety-ninth percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from

Event	Definitions
	the laboratory should be used. If the ninety-ninth percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the ninety-ninth percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. Creatine kinase-myocardial band (CK-MB) should be used if troponins are not available, and total creatine kinase (CK) may be used in the absence of CK-MB and troponin. For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL. Since it is not practical to stipulate the use of a single biomarker or assay, the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability. Since the prognostic significance of different types of MIs (eg, periprocedural MI versus spontaneous MI) may be different, outcomes for these subsets of subjects may be evaluated separately. c) ECG Changes Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves. ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy [LVH] and left bundle branch block [LBBB]) include: • ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women • ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1. The above ECG criteria illustrate patterns consistent with myocardial ischemia. In subjects with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings. • Criteria for pathological Q-wave – Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3 – Q-wave ≥0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)[c] • ECG changes associated with prior MI – Pathological Q-waves, as defined above

Event	Definitions
	– R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect • Criteria for prior MI: Any one of the following criteria meets the diagnosis for prior MI: – Pathological Q waves with or without symptoms in the absence of non-ischemic causes – Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause Pathological findings of a prior myocardial infarction
Hospitalization for Unstable Angina	Unstable angina requiring hospitalization is defined as: 6. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥10 minutes in duration occurring • at rest, or • in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity. AND 7. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available). AND 8. At least one of the following: a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH) • Transient ST elevation (duration <20 minutes) New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women. • ST depression and T-wave changes • New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or new T inversion ≥0.3 mV in two contiguous leads with prominent R wave or R/S ratio >1. b. Definite evidence of inducible myocardial ischemia event as demonstrated by: • an early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression prior to 5 mets OR • stress echocardiography (reversible wall motion abnormality) OR • myocardial scintigraphy (reversible perfusion defect), OR • magnetic resonance imaging (MRI; myocardial perfusion deficit under pharmacologic stress).

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td></td><td>• And believed to be responsible for the myocardial ischemic symptoms/signs.
c. Angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.
d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.
AND
Negative cardiac biomarkers and no evidence of acute MI</td></tr>
<tr><td>Transient Ischemic Attack (TIA)</td><td>TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction.</td></tr>
<tr><td>Stroke (Includes Ischemic Stroke, Hemorrhagic Stroke, Undetermined Stroke, or Stroke Disability)</td><td>Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.
A. Ischemic Stroke: Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.
B. Hemorrhagic Stroke: Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
C. Undetermined Stroke: Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.
Stroke Disability: Disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement:
<table>
<tr><th>Scale</th><th>Disability</th></tr>
<tr><td>0</td><td>No symptoms at all</td></tr>
<tr><td>1</td><td>No significant disability despite symptoms; able to carry out all usual duties and activities</td></tr>
<tr><td>2</td><td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td></tr>
<tr><td>3</td><td>Moderate disability; requiring some help, but able to walk without assistance</td></tr>
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<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td></td><td>
<table>
<tr><td>4</td><td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td></tr>
<tr><td>5</td><td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td></tr>
<tr><td>6</td><td>Dead</td></tr>
</table>
</td></tr>
<tr><td>Heart Failure (A HF event includes hospitalization for HF and may include urgent outpatient visits)</td><td>
A HF hospitalization is defined as an event that meets ALL of the following criteria:
1. The subject is admitted to the hospital with a primary diagnosis of HF
2. The subject’s length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
3. The subject exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
• Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
• Decreased exercise tolerance
• Fatigue
• Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol)
4. The subject has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
a. Physical examination findings considered to be due to HF, including new or worsened:
i. Peripheral edema
ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
iii. Pulmonary rales/crackles/crepitations
iv. Increased jugular venous pressure and/or hepatojugular reflux
v. S_3 gallop
vi. Clinically significant or rapid weight gain thought to be related to fluid retention
b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT pro-BNP) concentrations consistent with decompensation of HF (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In subjects with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
ii. Radiological evidence of pulmonary congestion
</td></tr>
</table>

Event	Definitions
	iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, ECG criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI]) OR iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2 Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events. 5. The subject receives initiation or intensification of treatment specifically for HF, including at least ONE of the following: a. Augmentation in oral diuretic therapy b. Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator) c. Mechanical or surgical intervention, including: i. Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart) ii. Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis) An urgent HF visit is defined as an event that meets all of the following: 6. The subject has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization (i.e. urgent outpatient visit) 7. All signs and symptoms for HF hospitalization (ie, symptoms and physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met 8. The subject receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.
Interventional Cardiology: Clinical Definitions	
Clinically-Driven Target Lesion Revascularization:	Revascularization is clinically-driven if the target lesion diameter stenosis is >50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following: a. A history of angina pectoris, presumably related to the target vessel

Event	Definitions
	b. Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel c. Abnormal results of any invasive functional diagnostic test [eg, coronary flow reserve (CFR) or fractional flow reserve (FFR)] Comment: Target lesion revascularization of a >70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically-driven. Comment: In the absence of QCA data or if a ≤50% stenosis is present, TLR may be considered clinically-driven by the Adjudication Committee (AC) if severe ischemic signs and symptoms attributed to the target lesion are present.
Non-Target Lesion and Non-Target Lesion Revascularization:	A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Non-Target Vessel and Non-Target Vessel Revascularization:	A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Percutaneous Coronary Intervention (PCI) Status:	a. Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of MI or death. For stable inpatients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the subject's clinical situation demands the procedure prior to discharge. b. Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Subjects who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation. c. Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a subject who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours. d. Salvage: The procedure is a last resort. The subject is in cardiogenic shock when the PCI begins (ie, the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) OR within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the subject has also received chest compressions or has been on unanticipated circulatory support (eg, intra-aortic balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).
Percutaneous Coronary Intervention (PCI):	Placement of an angioplasty guide wire, balloon, or other device (eg, stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, coronary flow reserve

Event	Definitions
	(CFR), or fractional flow reserve (FFR), insertion of a guide wire will NOT be considered PCI.
Procedural Success:	Achievement of <30 % residual diameter stenosis of the target lesion assessed by visual inspection or QCA and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory. Comment: For some device interventions (eg, balloon angioplasty), achievement of <50% diameter stenosis by visual inspection or QCA is an acceptable definition for procedural success.
Target Lesion:	Any lesion treated or attempted to be treated during the PCI with the study device. The target lesion includes the arterial segment treated with the study device (stent, in most cases) plus 5 mm proximal and 5 mm distal to the treatment site.
Target Lesion Failure (TLF):	The composite of ischemia-driven revascularization of the target lesion, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TLF.
Target Lesion Revascularization (TLR):	Any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the AC for review upon request.
Target Vessel:	A major native coronary artery (eg, left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) or bypass graft containing the target lesion. A native coronary artery target vessel includes the arterial segments upstream and downstream to the target lesion plus major side branches.
Target Vessel Failure (TVF):	The composite of ischemia-driven revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TVF.
Target Vessel, Non-Target Lesion, and Target Vessel, Non-Target Lesion Revascularization:	Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.
Target Vessel Revascularization (TVR):	Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.
Vascular Complications:	• Access site hematoma: Development of a new, localized collection of blood at a vascular access site sufficient to produce a palpable mass within 72 hours of a procedure.

<table>
<tr><th>Event</th><th>Definitions</th></tr>
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Arteriovenous fistula: Development of a new, unintended communication between an artery and a vein occurring at a vascular access site within 72 hours of a procedure.
Peripheral ischemia: Development of new arterial insufficiency sufficient to produce clinical signs or symptoms of ischemia (pallor, pain, paresthesia) distal to a vascular access site within 72 hours of a procedure.
Peripheral nerve injury: Development of new sensory or motor loss of peripheral nerve function from external nerve compression (eg, as a result of positioning during a procedure), or internal compression or direct nerve damage from the procedure, occurring within 72 hours of a procedure.
Pseudoaneurysm: Development of a new localized collection of blood with a persistent communication (neck) originating at a vascular access site and occurring within 72h of a procedure.
Retroperitoneal hemorrhage: Development of new bleeding into the retroperitoneal space originating at a vascular access site and occurring within 72 hours of a procedure.

</td></tr>
<tr><td colspan="2">Interventional Cardiology: Angiographic Definitions</td></tr>
<tr><td>Abrupt Closure:</td><td>New intra-procedural severely reduced flow (TIMI grade 0-1) within the target vessel that persists and requires intervention by stenting or other treatment, or results in MI or death. Abrupt closure requires an association with a vascular dissection, thrombus, or severe spasm at the treatment site or within the instrumented vessel.</td></tr>
<tr><td>Coronary Lesions Treated</td><td>
<table>
<tr><th>Coronary Artery Segments</th><th>Definitions</th></tr>
<tr><td>Right coronary artery ostium</td><td>Origin of the right coronary artery, including the first 3 mm of the artery</td></tr>
<tr><td>Proximal right coronary artery</td><td>Proximal portion of the right coronary artery, from the ostium of the right coronary artery to the origin of the first right ventricular branch (pRCA)</td></tr>
<tr><td>Mid right coronary artery</td><td>Middle portion of the right coronary artery, from the origin of the first right ventricular branch to the acute margin (mRCA)</td></tr>
<tr><td>Distal right coronary artery</td><td>Distal portion of the right coronary artery, from the acute margin to the origin of the posterior descending artery (dRCA)</td></tr>
<tr><td>Right posterior descending artery</td><td>In right dominant and mixed circulations, the vessel that runs in the posterior interventricular groove and supplies septal perforator branches (PDA)</td></tr>
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Event	Definitions	
	Posterolateral segmental artery	In right dominant circulations, the distal continuation of the right coronary artery in the posterior atrioventricular groove after the origin of the right posterior descending artery (PLSA)
	First right posterolateral branch	In right dominant circulations, the first posterolateral branch originating from the right posterior atrioventricular artery (RPL1)
	Second right posterolateral branch	In right dominant circulations, the second posterolateral branch originating from the right posterior atrioventricular artery (RPL2)
	Third right posterolateral branch	In right dominant circulations, the third posterolateral branch originating from the right posterior atrioventricular artery (RPL3)
	Posterior descending septal perforator	Septal perforator vessel originating from the posterior descending artery
	Right ventricular branch	Branch arising from the right coronary artery to supply the right ventricular wall (RV)
	Left main coronary artery ostium	Origin of the left coronary artery, including the first 3 mm of the artery
	Left main coronary artery body	Body of the left main coronary artery, from the ostium to the bifurcation (LM)
	Left main coronary artery bifurcation	Distal end of the left main, including the terminal 3 mm through the bifurcation of the left main into the left anterior descending and left circumflex arteries
	Left anterior descending artery ostium	Origin of the left anterior descending coronary artery, including the first 3 mm of the artery
	Proximal left anterior descending artery	Proximal portion of the left anterior descending coronary artery, from the ostium to the origin of the first septal (pLAD)
	Mid left anterior descending artery	Middle portion of the left anterior descending coronary artery, from the origin of the first septal artery to the origin of the third septal artery (mLAD)
	Distal left anterior descending artery	Distal portion of the left anterior descending coronary artery, from the origin of the third septal artery to the terminus (dLAD)
	First diagonal branch	First of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D1)
	First diagonal lateral branch	Branch of the first diagonal branch

Event	Definitions	
	Second diagonal branch	Second of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D2)
	Second diagonal lateral branch	Branch of the second diagonal branch
	Third diagonal branch	Third of the three longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D3)
	Third diagonal lateral branch	Branch of the third diagonal branch
	Anterior descending septal perforator	Septal perforator vessel originating from the left anterior descending artery to supply the interventricular septum
	Left circumflex artery ostium	Origin of the left circumflex coronary artery, including the first 3 mm of the artery
	Proximal left circumflex artery	Proximal portion of the left circumflex coronary artery, from the ostium to the origin (or the nominal location of) the first marginal branch (pLCX)
	Mid left circumflex artery	Middle portion of the left circumflex coronary artery, from the origins of (or nominal locations of) the first marginal to the second marginal (mLCX)
	Distal left circumflex artery	Distal portion of the left circumflex coronary artery, from the origin of (or the nominal location of) the second marginal to the terminus (in right dominant systems), or to the origin of the 1st left posterolateral in all other dominance systems (dLCX)
	First obtuse marginal branch	First of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM1)
	First obtuse marginal lateral branch	Branch of the first marginal branch
	Second obtuse marginal branch	Second of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM2)
	Second obtuse marginal lateral branch	Branch of the second marginal branch
	Third obtuse marginal branch	Third of the three longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM3)
	Third obtuse marginal lateral branch	Branch of the third marginal branch

<table>
<tr><th>Event</th><th>Definitions</th></tr>
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<table>
<tr><td>Left atrioventricular artery</td><td>In left dominant and mixed circulations, the distal continuation of the left circumflex coronary artery in the posterior atrioventricular groove</td></tr>
<tr><td>Left posterior descending artery</td><td>In left dominant circulations, the vessel that arises from the distal continuation of the left atrioventricular artery, travels in the posterior interventricular groove, and supplies septal perforator branches (LPDA)</td></tr>
<tr><td>First left posterolateral branch</td><td>In left dominant and mixed circulations, the first posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL1)</td></tr>
<tr><td>Second left posterolateral branch</td><td>In left dominant and mixed circulations, the second posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL2)</td></tr>
<tr><td>Third left posterolateral branch</td><td>In left dominant and mixed circulations, the third posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL3)</td></tr>
<tr><td>Ramus intermedius branch</td><td>Branch vessel whose origin bisects the origins of the left anterior descending and circumflex arteries (RI)</td></tr>
<tr><td>Ramus intermedius lateral branch</td><td>Branch of the ramus intermedius branch</td></tr>
</table>
</td></tr>
<tr><td>Dissection:</td><td>Based on the National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:
Grade A: Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance
Grade B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance
Grade C: Extraluminal cap with persistence of contrast after dye clearance from the lumen
Grade D: Spiral luminal filling defect with delayed but complete distal flow
Grade E: New persistent filling defect with delayed antegrade flow
Grade F: Non-A-E types with total coronary occlusion and no distal antegrade flow
Note: Grade E and F dissections may represent thrombus</td></tr>
<tr><td>Late Loss:</td><td>Minimum lumen diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the index procedure. MLDs are measured by QCA.</td></tr>
</table>

Event	Definitions
Minimum Lumen Diameter (MLD):	The mean minimum lumen diameter (typically measured in-lesion, in-stent, and in-segment) derived from two orthogonal views by QCA.
No Reflow:	An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.
Percent Diameter Stenosis (% DS):	The value calculated as 100 x (1 – MLD/RVD) using the mean values determined by QCA from two orthogonal views (when possible).
Reference Vessel Diameter (RVD):	Defined as the average of normal segments within 10 mm proximal and 10 mm distal to the target lesion from two orthogonal views using QCA.
Restenosis:	Re-narrowing of the vessel following the treatment of a prior stenosis • Binary restenosis: A diameter stenosis of > 50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 5 mm proximal and 5 mm distal to the site. • In-stent restenosis (ISR): A previously stented lesion with a > 50% diameter stenosis.
Thrombus (Angiographic):	A discrete, mobile, intraluminal filling defect with defined borders with or without associated contrast staining.
TIMI (Thrombolysis in Myocardial Infarction) Flow Grades:	• Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion. • Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence. • Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (eg, the opposite coronary artery or the coronary bed proximal to the obstruction). • Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery.
Vessels	• Left main coronary artery (LMCA) • Left anterior descending artery (LAD) with septal and diagonal branches • Left circumflex artery (LCX) with obtuse marginal branches • Ramus intermedius artery • Right coronary artery (RCA) and any of its branches • Posterior descending artery

Event	Definitions
	• Saphenous vein bypass graft(s) • Arterial bypass graft(s): Right internal mammary graft, left internal mammary graft, radial artery graft, and gastroepiploic artery graft.
Peripheral Vascular Intervention	
Peripheral Vascular Intervention (PVI):	Peripheral vascular intervention[d] is a catheter based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, percutaneous transluminal balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision. In general, the intention to perform percutaneous peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein. The target vessel(s) and the type of revascularization procedure (eg, surgical bypass, thrombectomy, endarterectomy, percutaneous transluminal angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.
Procedural Success:	In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a satisfactory final residual diameter stenosis by angiography at the end of the procedure (and without flow limiting dissection or hemodynamically significant translesional pressure gradient). The specific parameter for final percent residual stenosis is typically between <30% and <50%; selection of the appropriate percentage may vary depending upon the specific intervention applied, the vascular territory, and anticipated or desired therapeutic response. Procedural success also implies absence of in-hospital major adverse events (eg, death, stroke, myocardial infarction, acute onset of limb ischemia, need for urgent/emergent vascular surgery, and other procedure-specific major adverse events). The balloon inflation, stent placement, or other therapeutic intervention may be preceded by use of adjunctive devices (eg, percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, and chronic total occlusion crossing device), as predefined in the protocol.
Procedural Status: Non-Elective and Elective:	a. Non-Elective: Non-elective procedures include emergent and urgent procedures. A non elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the subject, urgency of the medical condition, or instability of the threatening lesion. – Emergent: A procedure that is performed immediately because of the acute nature of the medical condition (eg, acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment. – Urgent: An urgent procedure is one that is not an emergency but is required to be performed on a timely basis (≤24 hrs) (eg, a

Event	Definitions
	subject who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours). b. Elective: An elective procedure is one that is scheduled and is performed on a subject with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.
Target Lesion:	A target lesion is any vascular segment treated or attempted to be treated during the trial procedure with the index device. The target lesion is the treated segment starting 10 mm proximal and ending 10 mm distal to the index device or therapy (stent, balloon, atherectomy catheter, or aortic stent-graft).
Target Vessel:	A target vessel is any vessel (eg, non-cardiac or non-intracranial) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire length of native vessel upstream and downstream from the target lesion, including side branches. For the arteries of the leg, the vasculature is divided into 3 vessel "levels:" aorto-iliac, femoral-popliteal, and tibial-crural.
Non-Target Lesion and Non-Target Lesion Revascularization:	A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Non-Target Vessel and Non-Target Vessel Revascularization:	A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
Target Vessel, Non-Target Lesion and Target Vessel, Non-Target Lesion Revascularization:	Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.
Target Lesion Revascularization (TLR):	Target lesion revascularization is any repeat intervention of the target lesion (including 10 mm proximal and 10 mm distal to the index device, as target lesion is defined above) or surgical intervention/bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.
Target Vessel Revascularization (TVR):	Target vessel revascularization is any repeat intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.
Clinically-Driven Target Lesion Revascularization:	Clinically-driven target lesion revascularization is defined as target lesion revascularization performed due to target lesion diameter stenosis >50% AND either evidence of clinical or functional ischemia (eg, recurrent/progressive intermittent claudication, critical limb ischemia) OR recurrence of the clinical syndrome for which the initial procedure was performed. Clinically-driven target

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td></td><td>lesion revascularization occurs in the absence of protocol-directed surveillance ultrasound or angiography.</td></tr>
<tr><td>Vessel Patency:</td><td>Vessel patency at a given time point will be determined by the absence of clinically-driven target lesion revascularization and/or absence of recurrent target lesion diameter stenosis >50% by imaging (eg, invasive angiography or most commonly, duplex ultrasonography). If patency data are incorporated within the primary endpoint of a clinical trial, the angiographic images or duplex ultrasonographic images should be assessed by appropriate core laboratories and made available to the AC for review upon request.</td></tr>
<tr><td>Restenosis:</td><td>Re-narrowing of the artery following the treatment of a prior stenosis
Binary restenosis: A diameter stenosis of >50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 10 mm proximal and 10 mm distal to the site (or as otherwise defined by the protocol, as noted above).
In-stent restenosis (ISR): A previously stented lesion that has >50% diameter stenosis.</td></tr>
<tr><td colspan="2">Stent Thrombosis</td></tr>
<tr><td>Stent Thrombosis: Timing</td><td>Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the cardiac catheterization laboratory.
Stent Thrombosis: Timing
<table>
<tr><td>Acute stent thrombosis[1]</td><td>0-24 hours post stent implantation</td></tr>
<tr><td>Subacute stent thrombosis[1]</td><td>>24 hours – 30 days post stent implantation</td></tr>
<tr><td>Late stent thrombosis[2]</td><td>>30 days – 1 year post stent implantation</td></tr>
<tr><td>Very late stent thrombosis[2]</td><td>>1 year post stent implantation</td></tr>
<tr><td colspan="2">[1] Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0-30 days) will be used herein.
[2] Includes “primary” as well as “secondary” late stent thrombosis; “secondary” late stent thrombosis is a stent thrombosis after a target lesion revascularization.</td></tr>
</table></td></tr>
<tr><td>Stent Thrombosis Categories</td><td>1. Definite Stent Thrombosis
Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:
a. Angiographic confirmation of stent thrombosis[e]
The presence of a thrombus[f] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
Acute onset of ischemic symptoms at rest
New ischemic ECG changes that suggest acute ischemia</td></tr>
</table>

Event	Definitions
	– Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI) – Nonocclusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream – Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch). b. Pathological Confirmation of Stent Thrombosis: Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. 2. Probable Stent Thrombosis: Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases: a. Any unexplained death within the first 30 daysg b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause 3. Possible Stent Thrombosis: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial follow-up.

[a] The 30-day cut-off is arbitrary.
[b] 2012 Third Universal Definition of Myocardial Infarction.
[c] The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.
[d] Peripheral vascular disease includes veins, arteries, and lymphatics. However, for simplicity, this definition focuses on peripheral artery and venous interventions.
[e] The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
[f] Intracoronary thrombus.
[g] For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.
Source: "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials," dated August 20, 2014, and available at the CDISC website (http://www.cdisc.org/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020,%202014.pdf).

APPENDIX F. SUMMARY OF CHANGES: 747-304 PROTOCOL VERSION 6.0 TO PROTOCOL VERSION 7.0 (DATED: 16 JUN 2021)

Protocol 747-304 was revised to include the following information:

1) Reorganization and updates to the study objectives and related sections on overall assessments and statistics
2) Inclusion of Hepatic Safety Adjudication Committee and Renal Adjudication Committee for the adjudication of all events of potential hepatic injury and acute kidney injury, respectively. The protocol was updated to ensure these events will be provided to the DMC for inclusion in their review as well as added to the Safety Objectives to be assessed at the End of Study.
3) Updated process for the monitoring and management of potential DILI and updated the DILI algorithm and laboratory triggers to monitor hepatic injury
4) Clarification of language on PK sample collection following investigational product interruption or discontinuation and within 7 days of experiencing a serious adverse event.
5) Additional sections added to address monitoring and management of renal impairment and nephrolithiasis, hyperglycemia, and dyslipidemia. Additional education and assessments to identify intercurrent illness and/or potential adverse events was added.
6) Inclusion of local laboratory results and reference ranges into the eCRF
7) COVID-19-related changes to the protocol
8) The use of "suspected" was globally updated to "potential" throughout the protocol
9) Interactive web response system (IWRS) was updated to randomized and trial supply management system (RTSM) to align with new vendor terminology
10) Previous Summary of Changes for each protocol amendment removed. Moving forward, only the current Summary of Changes with be included.

The text deleted from Protocol Version 6.0 is crossed out and revised text in Version 7.0 is indicated in bold font in the following table. Each revision also includes a reason or justification for the change. Section numbers refer to Version 7.0 unless otherwise stated. Sections with extensive changes that are discussed elsewhere have been summarized rather than highlighting exact changes. Minor changes including typos or editorial revisions are not listed individually in the following table.

Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
Title Page	Sponsor Intercept Pharmaceuticals, Inc. ~~4760 Eastgate Mall~~ San Diego, CA 92121 USA	Sponsor Intercept Pharmaceuticals, Inc. **9520 Towne Centre Drive, Suite 200** San Diego, CA 92121 USA	Sponsor address updated to reflect new location
Sponsor's Approval	[redacted] [redacted] Clinical Development Intercept Pharmaceuticals, Inc.	[redacted] [redacted] Clinical Development Intercept Pharmaceuticals, Inc.	Sponsor wet signature approver updated to reflect change in personnel
Study Personnel Contact Information	Secondary Contact: [redacted] ~~PharmD, MS~~ [redacted] ~~PV Monitoring~~ Intercept Pharmaceuticals, Inc. Email: [redacted]	Secondary Contact: [redacted] **MD** [redacted] **Scientific Affairs** Intercept Pharmaceuticals, Inc. Email: [redacted] **Telephone** [redacted]	Secondary contact was updated to reflect change in personnel
Section 5.4.1 Section 23	NASH ~~is likely to be~~ the leading cause of liver transplant ~~by 2020~~, highlighting the need for development of effective therapies that may improve steatohepatitis and fibrosis, potentially delaying liver transplant or death.	NASH **has become one of** the leading causes of liver transplant **(Wong 2020, Younossi 2020)**, highlighting the need for development of effective therapies that may improve steatohepatitis and fibrosis, potentially delaying liver transplant or death. References: **Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014-2019. JAMA Netw Open. 2020 Feb;3(2):e1920294.** **Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic Steatohepatitis is the most rapidly increasing indication for liver transplantation in**	Updated the language and references to provide support for statement regarding current rate of liver transplantation

Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
		the United States. Clin Gastroenterol Hepatol. 2020 Jun 9.	
Section 5.5	Post-Marketing Cases of Liver Injury in PBC ~~Liver injury, liver decompensation, liver failure, and death have been reported in patients with moderate to severe hepatic impairment (CP Class B and Class C) when Ocaliva was dosed more frequently than recommended in labeling for such patients (up to 7 times the recommended dose). In addition, serious liver adverse events have been reported in the post marketing setting in OCA treated patients without cirrhosis or with mild liver impairment, both early in treatment and after months of treatment.~~ ~~Signs and symptoms reported in patients experiencing liver related adverse outcomes who received Ocaliva include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice, and liver decompensation~~. Clinical Study Experience Liver-related events … ~~Four cases of hepatic decompensation and potential drug induced liver injury (DILI) in the PBC program assessed as possibly related were examined by an independent hepatic adjudication committee. Although the subjects experienced progression of liver dysfunction while on OCA~~	**Post-Marketing Cases of Liver Injury in PBC** **In post-marketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in PBC subjects with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCA was dosed more frequently than the recommended starting dosage of 5 mg once weekly (ie, off-label use). Subjects who died due to hepatic complications generally had decompensated cirrhosis prior to treatment and were started on OCA 5 mg QD, which is 7-fold greater than the once weekly starting regimen in this population and considered to be a medication error.** **Based on a comprehensive review in 2017 of both existing and new clinical information, including more than 1300 patient-years of exposure and subjects with advanced disease, multiple analyses confirm lack of hepatotoxicity at the current recommended doses of OCA. The existing post-marketing evidence at that time was considered insufficient to confirm a causal relationship between exposure to OCA and the occurrence of hepatic decompensation and/or death. The majority of cases reported were for advanced PBC patients receiving doses inconsistent with dosing instructions in the label. Even in these cases, there is no clear evidence that the higher**	Known potential risks with investigational product were updated to reflect the language in the current version of the OCA Investigational Brochure

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	~~treatment, the committee concluded the pattern was consistent with progression of underlying disease rather than a DILI event~~. Analyses of liver-related safety information from NASH subjects treated with OCA demonstrate an overall hepatic safety profile consistent with PBC. There is no evidence to indicate a consistent, dose-dependent worsening of liver biochemistries at doses up to 25 mg, including ALT, AST or bilirubin. Modest increases in alkaline phosphatase (ALP) levels have occurred following treatment with OCA; however, ALP levels were generally within upper limits of normal. ALP elevations are generally not associated with a rise in gamma-glutamyl transferase (GGT), suggesting that these changes are unlikely to be due to cholestatic liver injury. ~~The incidence of liver related adverse events in NASH clinical studies overall was low. Events specifically reflective of hepatic decompensation in the NASH program was low with comparable incidence between OCA and placebo (2% OCA versus % placebo).~~ ~~Two~~ cases of hepatic decompensation have been reported as SUSARs, 1 of which resulted in death. ~~In the ongoing Phase 3 clinical Study 747-303, a NASH subject with no evidence of cirrhosis at Baseline presented with acute liver injury, acute kidney injury, hyperbilirubinemia, and a generalized vesicular rash, which required hospitalization. The Investigator assessed the events as severe, serious due to hospitalization,~~	**than recommended dosing frequency of OCA led to adverse outcomes.** **PBC is a chronic progressive liver disease, ultimately progressing to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, liver transplant, and/or death. Given that hepatic decompensation events are part of the natural history of PBC and patients with end stage disease are particularly vulnerable, it is often not possible to distinguish on a case level the hypothesized drug effects from the natural history of the disease.** **As a result, a boxed warning was added to the labeling in 2018 providing additional guidance on patient management for patients with decompensated cirrhosis as well as stronger dosing guidelines.** **A new label, approved on 01 June 2021, states that in the US, OCA is now contraindicated in PBC subjects with compensated cirrhosis with evidence of portal hypertension after a Newly Identified Safety Signal evaluation.** Clinical Study Experience Liver-related events … **In a pooled analysis of 3 completed placebo-controlled clinical trials in patients with primarily early-stage PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant hepatic adverse reactions and isolated elevations in liver**	

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	~~important medical events, and possibly related to the investigational product (remains blinded). In the ongoing Phase 2 open label extension phase of Study 747-209, a NASH subject with a history of NASH cirrhosis with hepatic impairment and presumptive evidence of portal hypertension reported events of severe diarrhea, jaundice, and unintended weight loss (30 lbs in approximately 1 month) approximately 5 months after initiating treatment with OCA 25 mg; OCA was discontinued at that time. The subject was subsequently hospitalized for acute renal failure and died due to renal failure and liver failure leading to cardiac arrest. The Investigator assessed both the event of acute renal failure and the event of liver failure as fatal in severity, serious, and unlikely related to investigational product~~. Pruritus Pruritus is an expected adverse event associated with OCA, particularly in subjects with cholestatic liver diseases such as PBC where pruritus is a common symptom of the disease. In PBC clinical studies, the incidence of pruritus was 68% for OCA-treated subjects compared with 40% in placebo-treated subjects. The majority of events have been reported as mild to moderate in severity and infrequently resulted in early discontinuation. The majority of subject's experiencing pruritus did not require an intervention for pruritus. The incidence and severity of pruritus have been shown to be dose	**biochemical tests per 100 patient exposure years (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.** Analyses of liver-related safety information from NASH subjects treated with OCA demonstrate an overall hepatic safety profile consistent with PBC. There is no evidence to indicate a consistent, dose-dependent worsening of liver biochemistries at doses up to 25 mg, including ALT, AST or bilirubin. Modest increases in alkaline phosphatase (ALP) levels have occurred following treatment with OCA; however, ALP levels were generally within upper limits of normal. ALP elevations are generally not associated with a rise in gamma-glutamyl transferase (GGT), suggesting that these changes are unlikely to be due to cholestatic liver injury. **In NASH clinical trials 9** cases of hepatic decompensation have been reported as SUSARs, 1 of which resulted in death. **The signs of hepatic decompensation included death due a hepatic event; MELD score ≥15; liver transplant; ascites; or an SAE of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.** **Of these events, one was considered unlikely related to OCA and 6 were considered possibly related to blinded treatment. The remaining**	

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	dependent, but there is no evidence of association with stage or progression of underlying disease. ~~In NASH clinical trials, AEs of pruritus were reported less frequently with OCA treatment relative to PBC. In the FLINT study, mild to moderate pruritus occurred in 23% of OCA-treated subjects compared with 6% of placebo-treated subjects and only 1 subject discontinued therapy as a result of pruritus.~~ …	**events were considered possibly related to treatment and concerned subjects receiving daily OCA 40 mg. One case describes a subject with an event of DILI, and a second case describes a subject with events of ascites and pruritus. In the case with ascites and pruritus, treatment was discontinued. Both subjects recovered from the events.** **Key hepatic findings in NASH subjects include the following:** **• In completed NASH clinical studies, cumulative on-study incidence rates for hepatic AEs and corresponding hazard ratios indicate that the rates of hepatic SAEs are not different across OCA and placebo groups. Although more events occurred in the OCA 25 mg group (6 [1%] subjects) than in the OCA 10 mg group (2 [<1%] subjects) or placebo group (2 [<1%] subjects), expert reviewers did not identify sufficient evidence supporting a consistent pattern of liver injury, and notably, the vast majority of cases were associated with confounding concomitant medications or severe intercurrent illness.** **• Given that the liver is the primary site of action for OCA safety and efficacy, liver concentrations for total OCA were predicted for subjects with hepatic impairment based on Child-Pugh Class score. A 1.1-fold increase in liver OCA exposure is predicted in subjects with mild hepatic impairment (Child-Pugh Class A); however, a 1.5- and 1.7-fold increase in liver concentrations of OCA are predicted for Child Pugh Class B**	

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		and C respectively, when compared to that of healthy subjects (Edwards et al 2016). In a hepatic impairment study (747-118) in NASH subjects with compensated liver cirrhosis (Child-Pugh Class A), plasma exposure was approximately 4- to 10-fold higher, and liver exposure was approximately 2-fold higher as compared to NASH subjects with liver fibrosis. OCA has not been evaluated in NASH subjects with decompensated cirrhosis (Child-Pugh Class B and Child-Pugh Class C). Pruritus Pruritus is an expected adverse event associated with OCA, particularly in subjects with cholestatic liver diseases such as PBC where pruritus is a common symptom of the disease. In PBC clinical studies, the incidence of pruritus was 68% for OCA-treated subjects compared with 40% in placebo-treated subjects. The majority of events have been reported as mild to moderate in severity and infrequently resulted in early discontinuation. The majority of subject's experiencing pruritus did not require an intervention for pruritus. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease. **Pruritus has also been observed in subjects with NASH. Across the three, long-term, double blind, placebo-controlled studies in subjects with liver fibrosis due to NASH (747-303, FLINT, and D8602001), the incidence of pruritus TEAEs was dose dependent and higher in the OCA 25 mg**	

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		group, as compared to the OCA 10 mg and placebo groups. The majority of pruritus TEAEs were mild to moderate in severity. The incidence of severe pruritus TEAEs was low, but higher in the OCA 25 mg group, as compared to the OCA 10 mg and placebo groups. The incidence of new or worsening pruritus TEAEs was highest early in the course of treatment (ie, first 3 months) and subsequently decreased over time. Consistent with the PBC experience, pruritus in subjects with NASH appeared to be manageable with temporary interruption of OCA treatment and the use of antipruritic medications. **…** **Glycemic Changes** **In NASH clinical studies, treatment with OCA was associated with a generally modest and transient rise in glycemic parameters (fasting plasma glucose, fasting serum insulin, and hemoglobin A1c (HbA1c), a well-established marker of long-term glycemic control) that occurred early (ie, within the first 3 months) and attenuated, returning to levels similar to placebo after approximately 6 months of treatment**	
Section 5.5.1	5.5.1. Risk/Benefit Profile of OCA in Subjects with NASH An independent data monitoring committee (DMC) has performed detailed reviews of individual subject and aggregate data from both the Phase 3 clinical outcomes study in subjects	5.5.1. Risk/Benefit Profile of OCA in Subjects with NASH An independent data monitoring committee (DMC) has performed detailed reviews of individual subject and aggregate data from both the Phase 3 clinical outcomes study in subjects with PBC	DMC recommendations were updated to reflect the language in the current version of the OCA Investigational Brochure

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	with PBC (Study 747-302) and the Phase 3 pivotal studies in subjects with NASH fibrosis (Study 747-303) and NASH cirrhosis (Study 747-304) on a quarterly basis, in an unblinded fashion, and in closed sessions (without the Sponsor's participation). ~~In the quarterly DMC meetings to date, the DMC has recommended the studies continue without modification.~~ Following a request from the FDA, an ad hoc DMC review was held and the DMC recommended that: • For subjects in Study 747-303, investigational product should be interrupted in subjects who experience symptomatic cholelithiasis and/or cholecystitis. The Sponsor decided to implement the DMC recommendations across the NASH program. In summary, based on the robust efficacy of OCA observed in PBC and NASH clinical studies, including improvements in liver biochemistry, fibrosis, and key histological features of NASH, as well as the overall safety profile of OCA (in >2300 healthy subjects and subjects with chronic liver diseases), the benefit-risk profile is favorable.	(Study 747 302) and the Phase 3 pivotal studies in subjects with NASH fibrosis (Study 747-303) and NASH cirrhosis (Study 747-304) on a quarterly basis, in an unblinded fashion, and in closed sessions (without the Sponsor's participation). Following a request from the FDA, an ad hoc DMC review was held, and the DMC recommended that: • For subjects in Study 747-303, investigational product should be interrupted in subjects who experience symptomatic cholelithiasis and/or cholecystitis. **In a subsequent DMC review, the DMC recommended that:** **• For subjects in Study 747-303, investigational product should be permanently discontinued in subjects diagnosed with acute pancreatitis.** The Sponsor decided to implement the DMC recommendations across the NASH program. In summary, based on the robust efficacy of OCA observed in PBC and NASH clinical studies, including improvements in liver biochemistry, fibrosis, and key histological features of NASH, as well as the overall safety profile of OCA (in >2300 healthy subjects and subjects with chronic liver diseases), the benefit-risk profile is favorable.	
Synopsis Section 6 Section 12	6. STUDY OBJECTIVES AND PURPOSE 6.1. Primary Objectives The primary objectives are to evaluate the effects of OCA treatment compared with placebo on:	6. STUDY OBJECTIVES AND PURPOSE 6.1. Primary Objectives **Assessed at the End of the Double-Blind Phase** The primary objectives are to evaluate the effects of OCA treatment compared with placebo on:	Objectives were reorganized into Secondary, Exploratory, PK/PD, and Safety as well as Primary for the OLE to more accurately

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	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to ~~Month 18~~ 6.2. Secondary Objectives The secondary objectives are to evaluate the effects of OCA treatment compared with placebo on: ~~• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 2 stages using Ishak scoring criteria from Baseline to Month 18~~ • Histological changes in fibrosis, including: (1) improvement, (2) no ~~worsening, and (3) progression~~ from Baseline to ~~Month 18~~ using the ~~following criteria, as appropriate:~~ - NASH CRN scoring system ~~- Ishak scoring criteria~~ ~~- Laennec staging system~~ • Resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to ~~Month 18~~	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to **the end of the Double-Blind Phase** 6.2. Secondary Objectives **Assessed at the End of the Double-Blind Phase** The secondary objectives are to evaluate the effects of OCA treatment compared with placebo on: • Resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to **the end of the Double-Blind Phase** • **Resolution of** NASH based on **pathologist's** overall **histopathologic** interpretation **of the presence or absence** of definite NASH from Baseline to **the end of the Double-Blind Phase** • Histological changes in fibrosis, including: (1) improvement, **and** (2) no **change**, from Baseline to t**he end of the Double-Blind Phase** using the NASH CRN scoring system • Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint): - Death (all cause)	capture study objectives. "Month 18" was replaced with "end of double-blind phase" to reflect biopsies that may have occurred at Month 12 (through protocol Version 4) and Month 18 Histology objectives were updated to reflect study population (ie removal of progression in fibrosis stage 4 population) and new central histology method, which will only include NASH CRN scoring. Additional assessments for adjudicated events of acute kidney injury and hepatic injury were added to align with the initiation of these committees

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	• NASH ~~resolution~~ based on overall ~~pathologist~~ interpretation ~~(resolution~~ of definite NASH) from Baseline to ~~Month 18~~ • Histological improvement in fibrosis by at least 1 stage and improvement in NAS by at least 2 points with at least 1 point improvement each for hepatocellular ballooning and lobular inflammation, using the NASH CRN scoring system, from Baseline to ~~Month 18~~ *[moved to exploratory]* • Improvement in each ~~key~~ histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning), using the NASH CRN scoring system, from Baseline to ~~Month 18~~ *[moved to exploratory]* • Change in NAS from Baseline to ~~Month 18~~ *[moved to exploratory]* ~~• Change in steatosis, activity, and fibrosis (SAF) score from Baseline to Month 18~~ • Change in morphometric assessment of quantitative collagen (assessed as percent collagen area [PCA]) from Baseline to ~~Month 18~~ *[moved to exploratory]* • Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint): - Death (all cause) - Liver transplant - MELD score ≥15	- Liver transplant - MELD score ≥15 - Worsening of CP score (by at least 2 points) - Hospitalization (as defined by a stay of ≥24 hours) for: • Variceal bleed • Hepatic encephalopathy (as defined by a West Haven score of ≥2) • Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) - Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) - HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy [redacted]	

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	- Worsening of CP score (by at least 2 points) - Hospitalization (as defined by a stay of ≥24 hours) for: • Variceal bleed • Hepatic encephalopathy (as defined by a West Haven score of ≥2) • Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) - Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) • ~~Occurrence of individual components of outcome events~~ • ~~Occurrence of~~ HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy • The ~~effect of OCA treatment compared to placebo on the~~ following ~~additional~~ measures and markers -*[moved to exploratory]*: - Liver biochemistry and synthetic function - Metabolic parameters - Inflammation - Apoptosis and necrosis	[redacted]	

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	~~- Cardiovascular safety (including adjudicated cardiovascular events)~~ - Health-related quality of life (eg, patient reported outcomes) - Standardized generic measure of health status for the assessment of health utilities - Noninvasive assessments of liver disease assessed by serum markers and imaging tests - Disease progression as assessed by MELD ~~and CP~~ scores • The effect of OCA treatment on FXR activation -*[moved to PK/PD]* • The PK of OCA and its conjugates *[moved to PK/PD]* • The PK/PD relationships of OCA and its conjugates *[moved to PK/PD]* • The effect of OCA treatment on liver function using HepQuant SHUNT (conducted at US sites where capable) *[moved to exploratory]* • Safety and tolerability *[moved to safety]* ~~Additional Secondary~~ Objective (Assessed at the End of the Open-Label Extension [OLE]) • To evaluate longer-term safety and tolerability ~~and efficacy~~ of OCA	[redacted] **6.4. PK/PD Objectives Assessed at the End of the Double-Blind Phase** • The effect of OCA treatment on FXR activation *[moved from Secondary]* • The PK of OCA and its conjugates *[moved from Secondary]* • The PK/PD relationships of OCA and its conjugates *[moved from Secondary]* **6.5. Safety Objectives Assessed at the End of the Double-Blind Phase** • **To evaluate the** safety and tolerability **of OCA treatment compared to placebo** *[moved from Secondary]* • **The effect of OCA treatment compared to placebo on the following additional measures and markers**: - **Markers of cardiovascular safety**	

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		- **Incidence of adjudicated cardiovascular events** - **Incidence of adjudicated acute kidney injury events** - **Incidence of adjudicated events of hepatic injury** • **6.6. Primary** Objectives Assessed at the End of the Open-Label Extension (OLE) • To evaluate **and summarize** the longer-term safety and tolerability of OCA treatment **• To summarize the effects of OCA treatment on the occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint):** - **Death (all cause)** - **Liver transplant** - **MELD score ≥15** - **Worsening of CP score (by at least 2 points)** - **Hospitalization (as defined by a stay of ≥24 hours) for:** • **Variceal bleed** • **Hepatic encephalopathy (as defined by a West Haven score of ≥2)** • **Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)**	

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		- **Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)** - **HCC as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy** [redacted]	

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Section 7.1.2, Table 1 Table 2	Schedule of Study Procedures For Clinical and Laboratory Evaluations – All Subjects • Additional urinalysis collection was added to the OLE Month 6 visit • Additional row was added for "**Evaluate Signs and Symptoms of Intercurrent Illness and/or Potential Adverse Events (Appendix C)**" o Double-Blind Phase: Occurs at Day 1 and all remaining study visits o OLE phase: Occurs at all study visits Footnotes: [y] **When a subject completes a liver biopsy as part of the EOT visit during the Double-Blind Phase, and remains in the study, a second biopsy is not required at the Month 18 Visit** OLE Phase: For Clinical Evaluations – For Subset of Subjects Footnotes: [d] **The OLE ICF may be obtained as early as Month 15 of the Double-Blind Phase.**		Schedule of study procedures was updated to reflect changes to renal monitoring including the frequency of the urinalysis to occur semi-annually Footnote added to clarify how early subjects may sign the ICF for the OLE and to clarify when a biopsy should be collected if EOT occurs prior to the Month 18 Visit
Section 7.4.1	Subjects will be evaluated at study visits for potential signs and symptoms of hepatic injury or decompensation: Signs and Symptoms of Hepatic Injury or Decompensation: • Specific signs and symptoms of liver impairment: 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)~~	**The Investigator will educate each subject about recognizing the signs and symptoms of suspected hepatic injury or decompensation and instruct each subject to contact the study site to report the onset of any new or worsening signs and symptoms during the study. The Investigator will instruct subjects to seek immediate medical attention if they experience signs or symptoms of hepatic injury or decompensation.** **Appendix C provides guidance for review of signs and symptoms of hepatic injury or decompensation described below to be evaluated**	Instructions added to encourage subjects to seek immediate medical attention Symptoms updated to reflect changes in DILI algorithm and for consistency with Appendix C

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	• More general signs and symptoms of ascites and encephalopathy: confusion, swelling of the legs or abdomen • Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite • Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea ~~for more than 4 days~~) and should be an indication for prompt investigational product interruption and complete subject evaluation Other Symptoms: • New or worsening pruritus • ~~Worsening of renal function or likely dehydration~~	**at each study visit, or as frequently as needed per Investigator's discretion.** Subjects will be evaluated at study visits for potential signs and symptoms of hepatic injury or decompensation: Signs and Symptoms of Hepatic Injury or Decompensation: • Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark] **severe fatigue, right upper quadrant pain, rash, eosinophilia** • More general signs and symptoms of ascites and encephalopathy: swelling of the legs or abdomen, confusion, **or abrupt abnormal behavior**, swelling of the legs or abdomen • Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite • Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea) and should be an indication for prompt investigational product interruption and complete subject evaluation Other Symptoms: • New or worsening pruritus • **Decreased urine output, urine color change, dizziness, lethargy**	

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Section 7.4.2	Liver biochemistr~~y~~ will be evaluated to assess biochemical triggers that will prompt an immediate reevaluation of subjects. Thus, these assessments will be performed at: • Each protocol-specified visit • Unscheduled visits for any safety follow-up as appropriate 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 ~~i~~nvestigator will obtain the laboratory results and the laboratory normal ranges. Of note, the Baseline result is the average of results from Screening Visits 1 and 2, Day 1, and any unscheduled visit that took place between Screening Visit 1 and the Day 1 Visit. The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and potentially a complete subject evaluation (depending on the repeat result) are summarized in Table 3. … If any subject meets the triggering threshold limits ~~for either conjugated bilirubin or creatinine~~, investigational product should be	**Events of potential as hepatic injury will be reviewed and adjudicated by the Hepatic Safety Adjudication Committee (HSAC), as described in Section 17.14. The specific criteria for identification and adjudication of potential hepatic injury events are described in the HSAC charter.** Liver biochemistr**ies** will be evaluated to assess biochemical triggers that will prompt an immediate reevaluation of subjects. Thus, these assessments will be performed at: • Each protocol-specified visit • Unscheduled visits for any safety follow-up as appropriate 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 **laboratory is required**. In these cases, the **I**nvestigator will obtain the laboratory results and the laboratory normal ranges. Of note, the Baseline result is the average of results from Screening Visits 1 and 2, Day 1, and any unscheduled visit that took place between Screening Visit 1 and the Day 1 Visit. **All local laboratory data, including the reference ranges, are to be collected and entered in the eCRF within 2 days of receiving the results. For guidance on alternative processes under which subjects may**	Process for identifying potential hepatic injury and the action taken with IP was updated to align with published guidance

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	immediately interrupted (see Section 7.6 for dosing modifications). ~~For the remaining liver biochemistry assessments, if a subject meets the upper threshold limits, the laboratory assessment should be repeated in 2 to 3 days (with the exception of ALP, which should be repeated in 7 days).~~ If a repeat laboratory test cannot be performed within ~~2 to 3~~ days, the subject should be instructed to interrupt investigational product until repeat ~~lab~~ results have been reviewed. • If on repeat evaluation, ~~values~~ are normal or ~~returned or trended back to prior values~~, no dosing modifications are required and the subject should continue to be monitored. • If on repeat evaluation, ~~values~~ remain ~~above the specified threshold~~, investigational product ~~should~~ be interrupted ~~(see Section 7.6 for dosing modifications). In this case, a medical history and physical exam should be conducted and AE information (including signs and symptoms of liver injury as described in Section 7.4.1) collected.~~ The medical monitor should be promptly contacted upon awareness for consultation regarding management of the subject. ~~If symptoms persist or repeat testing shows persistent abnormality as described above, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening~~. Subjects should, wherever possible, come back to the site. It may be difficult for subjects who are distant from their study site to return to the	**complete the protocol-specified assessments under COVID-19 restrictions refer to Section 10. Local laboratory visits in conjunction with remote (telemedicine) visits are specifically encouraged in lieu of on-site visits where subject's safety is of concern (eg, adverse event monitoring).** The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and potentially a complete subject evaluation (depending on the repeat result) are summarized in Table 3. … If any subject meets the triggering threshold limits **indicated in Table 3 and experiences signs or symptoms of hepatic injury (severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, eosinophilia) or events of decompensation (varices hemorrhage, hepatic encephalopathy, or ascites), which can be presenting features of DILI in subjects with cirrhosis,** investigational product should be immediately interrupted (see Section 7.7 for dosing modifications). **If no signs or symptoms of hepatic injury or decompensation are present, but liver biochemistries are above the triggering threshold limits, the subject should either interrupt investigational product or laboratory assessments including creatine phosphokinase (CPK) should be repeated within 2-4 days**	

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	site promptly. Such subjects ~~can~~ have repeat (or any safety) laboratory tests performed at a local laboratory, but normal laboratory ranges and the results should be made available to the Investigator, ~~and redacted copies provided to the Sponsor~~. It should be noted that it is difficult to recognize every potential marker of hepatic ~~or renal~~ deterioration. 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 artefactual; 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.	**according to the threshold limits specified in Table 3**. If a repeat laboratory test cannot be performed within **7** days **of receiving results**, the subject should be instructed to interrupt investigational product until repeat **laboratory** results have been reviewed. **If investigational product is interrupted, laboratory assessments including CPK should be repeated within 2-4 days, a PK sample must be collected (within 7 days), and close monitoring should be initiated (repeat labs and physical exam should occur as often as deemed appropriate by the Investigator and these data should be entered in the eCRF within 2 days of receiving results). In subjects with signs or symptoms of hepatic injury or decompensation, the Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject.** • If on repeat evaluation **in subjects who did not have investigational product interrupted (eg, those that had no signs and symptoms and lower severity) liver biochemistries** are normal **or below threshold** values, no dosing modifications are required and the subject should continue to be monitored **closely**. • If on repeat evaluation, **liver biochemistries** remain **elevated (see Table 3)**, investigational product **must** be interrupted **for a minimum of 30 days, a PK sample must be collected (within 7 days of receiving results), and close monitoring**	

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		should be initiated (repeat laboratory testing and physical exam should occur as often as deemed appropriate by the Investigator and these data should be entered in the eCRF within 2 days of receiving results). The Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject. **In any subject for whom interrupted investigational product for reasons other than the inability to promptly repeat laboratory testing (within 7 days) for non-safety reasons, a rechallenge may be considered after a minimum of 30 days if liver enzymes return to below threshold values, there are no symptoms, lab abnormalities are determined not to be due to DILI, and if approved by the Medical Monitor and Investigator. If investigational product is restarted after 30 days, liver biochemistries should be repeated within 2 to 4 days and close monitoring should be continued.** **If the liver enzymes do not return to below threshold values after 30 days and the Investigator considers that the event has not resolved, the Investigator should consult with the Medical Monitor to determine a treatment plan. This may include continuing close monitoring with interruption or discontinuing investigational product.** **For all subjects who investigational product is interrupted or discontinued, and close monitoring is initiated, a follow-up assessment of**	

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		the subject's status should be performed at study completion. Subjects should, wherever possible, come back to the site. It may be difficult for subjects who are distant from their study site to return to the site promptly. Such subjects **must** have repeat (or any safety) laboratory tests performed at a local laboratory, but normal laboratory ranges and the results should be made available to the Investigator. **All local laboratory data, including reference ranges, should be entered in the eCRF within 2 days of receiving the results. For guidance on alternative processes under which subjects may complete the protocol-specified assessments under COVID-19 restrictions refer to Section 10.** It should be noted that it is difficult to recognize every potential marker of hepatic deterioration. 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 artefactual or may clearly be explained for a particular subject as due to pre-existing conditions or circumstances unrelated to their liver function or the study; accordingly, Investigators may be allowed to implement an alternate follow-up procedure, based on their medical judgement, but only after documented consultation and agreement with the Sponsor's Medical Monitor. **Specific aspects of the Potential DILI Management Algorithm may be adjusted, in**	

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		which case specific guidelines will be provided to the sites for implementation.	
7.4.2, Figure 2	Figure 2: ~~Suspected~~ **Potential** DILI Management Algorithm for Study 747-304 *The following major changes were made to the figure:* • *"Conjugated bilirubin/creatinine" was replaced with "presence of signs and symptoms of hepatic injury or events of decompensation", which if present leads to immediate IP interruption and initiation of close monitoring* • *An additional step was added to confirm if the threshold met from Table 2 is a lower severity, as noted in the footnote.* • *An additional box (with footnote) was added below interruption of IP to highlight the importance and timeliness of PK sample collection and to clarify that close monitoring requires a physical exam and repeat biochemistry labs* • *Footnotes were updated to reflect the new proposed algorithm*		
Section 7.4.2, Table 3	Table 3: Liver Laboratory Criteria for Monitoring for ~~Suspected~~ **Potential** Hepatic Injury ~~or Decompensation~~ *Existing table and footnotes were replaced with new criteria and is updated to reflect updated threshold criteria, and guidance on PK sampling, use of local labs, and monitoring.*		
Section 7.4.3.1	Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which ~~will populate from the central laboratory~~. The relationship of CP Score to disease progression is as follows: CP score 5 6 = CP Class A; CP Score 7-9 = CP Class B; CP Score ≥10 = CP Class C.	Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which **should be collected at the same visit**. The relationship of CP Score to disease progression is as follows: CP score 5 6 = CP Class A; CP Score 7-9 = CP Class B; CP Score ≥10 = CP Class C.	Language was added to clarify that labs required to calculate CP score should be collected at the same visit.
Section 7.4.4	*Version 6 Section 7.7 Close Observation* At a minimum, the following assessments should be conducted at each study visit:	*Version 7 Section 7.4.4 Close Observation* At a minimum, the following assessments should be conducted at each study visit:	The close observation section is specific to potential hepatic injury and was therefore reorganized

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	• ~~Physical~~ exam and thorough review of subject reported signs and symptoms (Appendix C), … In addition, a pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any subject who develops an AE of hepatic injury or decompensation …	• Exam and thorough review of subject-reported signs and symptoms **of hepatic injury or decompensation** (Appendix C), … In addition, a pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any subject who develops an AE of hepatic injury or decompensation **or interrupts investigational product due to suspected hepatic injury (Section 7.4.2).** **…** **For all subjects who investigational product is interrupted or discontinued, and close monitoring is initiated, a follow-up assessment of the subject's status should be performed at study completion.**	back into this section header Updated based on actions taken with IB due to potential hepatic injury Inclusion of follow-up assessment per guidance in DILI algorithm
Section 7.5.1	NASH is associated with several known risk factors for cholelithiasis, such as obesity, type 2 diabetes, and other metabolic abnormalities. The prevalence of gallstone disease in NASH is higher than in the general population. The majority of gallstones are asymptomatic and may never become symptomatic. Because symptomatic events of cholelithiasis and/or cholecystitis may develop in subjects with or without a known history of gallstones, it is important that all subjects be (1) monitored for signs and symptoms suggestive of gallstone disease and (2) counseled to recognize and seek immediate medical attention if they experience	NASH is associated with several known risk factors for cholelithiasis, such as obesity, type 2 diabetes, and other metabolic abnormalities. The prevalence of gallstone disease in NASH is higher than in the general population. The majority of gallstones are asymptomatic and may never become symptomatic (**Sakorafas 2007, Stinton 2012**). Because symptomatic events of cholelithiasis and/or cholecystitis may develop in subjects with or without a known history of gallstones, it is important that all subjects be (1) monitored for signs and symptoms suggestive of gallstone disease and (2) counseled to recognize and seek immediate medical attention if they experience symptoms suggestive of cholelithiasis and/or cholecystitis.	Clarification added to capture when subjects are allowed to re-initiate IP

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	symptoms suggestive of cholelithiasis and/or cholecystitis. ~~If a subject experiences symptoms suggestive of cholelithiasis and/or cholecystitis, s/he should undergo a complete evaluation consistent with the local standard of care, be assessed for appropriate treatment, including potential indication for surgery (eg, cholecystectomy), and be monitored until resolution of clinical signs and symptoms.~~ ~~If symptomatic cholelithiasis and/or cholecystitis is diagnosed, investigational product should be interrupted (see Section 7.7).~~	**Subjects who develop signs or symptoms suggestive of symptomatic cholelithiasis and/or complications related to gallstone disease (eg, cholecystitis) should have investigational product interrupted while undergoing further evaluation consistent with the local standard of care and management until complete resolution, including potential surgical intervention.** **Post-cholecystectomy, subjects should be monitored for full resolution and may resume investigational product after approval from the Investigator and Medical Monitor (see Section 7.7).** **If upon surgical evaluation, it is deemed that the subject does not need to undergo surgery, the subject may re-initiate investigational product upon resolution of symptoms and approval from the Investigator and Medical Monitor.** **References:** **Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. Dig Dis Sci 2007 May; 52:1313-25.** **Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver. 2012 Apr;6(2):172-87.**	
Section 7.5.2	Because symptoms of acute pancreatitis and acute cholecystitis may be similar, subjects	Because symptoms of acute pancreatitis and acute cholecystitis may be similar, subjects presenting	Revised to emphasize that data used to

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Section 16.1.12	presenting with significant upper abdominal pain with nausea, vomiting, ~~or~~ fever should be evaluated for both cholecystitis and pancreatitis, consistent with the local standard of care (eg, amylase and lipase laboratory tests and/or imaging assessments). Investigational product must be permanently discontinued in any subject diagnosed with treatment-emergent acute, or nonacute (chronic or recurrent) pancreatitis (see Section 7.7). The evidence used to diagnose pancreatitis, including symptoms, laboratory test results, and/or imaging results, ~~should~~ be collected. 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 of treatment-emergent acute or nonacute pancreatitis.	with significant upper abdominal pain with nausea, vomiting, fever, **or jaundice** should be evaluated for both cholecystitis and pancreatitis, consistent with the local standard of care (eg, amylase and lipase laboratory tests and/or imaging assessments). Investigational product must be permanently discontinued in any subject diagnosed with treatment-emergent acute, or nonacute (chronic or recurrent) pancreatitis (see Section 7.7). The evidence used to diagnose pancreatitis, including symptoms, laboratory test results, and/or imaging results, **must** be collected. 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 **local** standard of care. The Investigator should contact the Medical Monitor upon awareness of treatment-emergent acute or nonacute pancreatitis.	diagnose pancreatitis must be collected
Section 7.6	*New Section*	**7.6. Monitoring for Renal Impairment and Nephrolithiasis** **7.6.1. Renal Impairment** **AKI is a serious medical condition that may lead to chronic kidney disease or kidney failure; therefore, it is important to identify and monitor subjects for signs or symptoms suggestive of AKI for appropriate management. Investigators are instructed to evaluate for symptoms suggestive of AKI such as new onset fatigue/asthenia, nausea,**	Guidance provided on monitoring and actions for IP interruption and PK sample collection for renal impairment and nephrolithiasis

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		or confusion and to assess signs such as decreased skin turgor (dehydration), increased heart rate, lower extremity edema, decreased urine output or dark urine at each visit. **As AKI is defined by an abrupt decrease in renal function, the Sponsor recognizes that local labs will be required to be recorded as well as all central lab data (scheduled or unscheduled visits) to adequately capture events. Repeat laboratory assessments should include albumin, serum chemistry (creatinine, BUN, electrolytes), urinalysis with microscopic examination, and assessment of estimated glomerular filtration rate (eGFR). All local laboratory data, including reference ranges, are required to be entered in the eCRF within 2 days of receiving results.** **The threshold criteria used to identify and monitor subjects for potential renal impairment and the actions to be taken with investigational product are outlined in Figure 3.** **Baseline serum creatinine values, which will inform the subsequent decisions on monitoring for and management of renal injury, are defined as the average of serum creatinine values from the two most recent study visits (scheduled and unscheduled), that are not associated with a renal-related AE or an acute increase.** **…** **If a subject meets the threshold criteria, a prompt re-evaluation (within 48 hours) should take place. Subjects should, when possible,**	

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		return to the study site for re-evaluation. It may be difficult for subjects who are distant from their study site to return to the site promptly. Such subjects must have repeat (or any safety) laboratory tests performed at a local laboratory, but the laboratory reference ranges and the results should be made available to the Investigator. All local laboratory data, including reference ranges, should be entered into the eCRF within 2 days of receiving the results. • **If on repeat testing, serum creatinine has returned to below threshold values, no dosing modifications are required.** • **If on repeat testing serum creatinine remains elevated, a comprehensive evaluation including the subject's recent medical history, changes in medication, health status, and intercurrent illness should be conducted. If no alternative cause of serum creatinine elevation can be identified investigational product should be interrupted and close monitoring should be initiated. Close monitoring includes repeat labs and physical exam, which should occur as often as deemed appropriate by the Investigator, and these data should be entered in to the eCRF within 2 days of receiving results. If deemed appropriate by the Investigator, the subject may be referred to a nephrologist.**	

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		In any subject for whom investigational product is interrupted for reasons other than inability to promptly repeat laboratory assessments for non-safety reasons: • **The event will be treated as a potential case of AKI and will be sent for review and adjudication by the Renal Adjudication Committee (described in Section 17.11.2). The specific criteria for identification and adjudication of potential AKI events are described in the Renal Adjudication Committee charter.** • **A PK sample must be collected with 7 days of investigational product interruption. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.** • **A rechallenge may be considered after a minimum of 30 days if serum creatinine returns to below threshold values and if approved by the Medical Monitor and Investigator. If serum creatinine remains above threshold values after 30 days, the subject should be referred to a nephrologist for further evaluation.** **7.6.2. Nephrolithiasis** **The development of signs or symptoms suggestive of kidney stones (nephrolithiasis) should be monitored. Standard of care including adherence to recommended dietary measures, adequate fluid intake, and other measures**	

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		prescribed should be employed to prevent recurrent episodes of kidney stones (Pearle 2014). Subjects should be asked if they have experienced symptoms of nephrolithiasis (evidence of hematuria, flank or lower abdominal pain, nausea, vomiting, fever, or chills). Nephrolithiasis should be considered in subjects with evidence of microscopic hematuria without other symptoms. **Subjects who develop kidney stones during the study will be further evaluated according to guidelines to collect serum electrolytes, uric acid, and a urinalysis with microscopic examination (Pearle 2014). All local laboratory data, including reference ranges, should be entered into the eCRF within 2 days of receiving the results. Every effort should be made to collect the kidney stone for analysis. Subjects should be referred to a urologist or nephrologist for further evaluation of the nephrolithiasis, including the etiology as appropriate.** Reference: **Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA Guideline. J Urol. 2014;192:316-24.**	
Section 7.6, Figure 3	Figure 3: Algorithm for Monitoring Subjects for Potential Renal Impairment. New figure clarifies creatinine threshold and the steps taken by the Investigator to monitor subjects with potential acute kidney injury including repeat testing, investigational product interruption, and monitoring.		

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Section 7.7	Subjects can be temporarily or permanently discontinued from investigational product by the Investigator at any time for clinical safety concerns. … Investigational product should not be interrupted in the following instances: 1) in subjects who previously experienced an event of symptomatic cholelithiasis and/or cholecystitis and in whom symptoms have fully resolved at the present time while on investigational product; ~~2) in subjects who experience an event that is not symptomatic (such as an incidental finding of gallstones during an ultrasound exam); 3) in subjects who have already undergone a cholecystectomy following a prior event of cholelithiasis or cholecystitis (and who have no symptoms suggestive of retained or recurrent bile duct stones);~~ or 4) in subjects who have a medical history of pancreatitis and have not experienced a recurrence of pancreatitis since enrollment into the study.	Subjects can be temporarily or permanently discontinued from investigational product by the Investigator at any time for clinical safety concerns. **If investigational product is temporarily or permanently discontinued, a PK sample must be collected within 7 days. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.** … Investigational product should not be interrupted in the following instances: 1) in subjects who **experience an event that is not symptomatic (such as an incidental finding of gallstones during an ultrasound exam); 2) in subjects who** previously experienced an event of symptomatic cholelithiasis and/or cholecystitis **and have either undergone a cholecystectomy (and have no symptoms suggestive of retained or recurrent bile duct stones) or upon surgical consultation does not need to undergo surgery**, and in whom symptoms have fully resolved at the present time while on investigational product; or **3**) in subjects who have a **past** medical history of pancreatitis and have not experienced a recurrence of pancreatitis since enrollment into the study.	Added PK sample collection to better understand exposure-response relationship. Reorganization of reasons IP should not be interrupted for clarity and to align with additional changes in Section 7.5.1
Section 7.7, Table 5	Table 5: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge *The criteria for Dose Interruption and its related footnotes were updated to reflect changes in monitoring for renal impairment, hepatic injury, cholelithiasis and/or cholecystitis. Rechallenge for gastroenteritis and AE categorized as ≥Grade 4 in severity, was updated to provide clear guidance on dosing*		
Section 7.7 Section 8.2.2	Prior to restarting investigational product after a prolonged interruption (ie, longer than ~~1~~ month [+2 weeks]), the subject must be reconsented.	Prior to restarting investigational product after a prolonged interruption (ie, longer than **3** months [+2 weeks]), the subject must be reconsented **and**	Interval for re-consenting subjects was extended to allow

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	~~New baseline procedures must be performed if the interval from the last visit was more than 1 month (+2 weeks) during the study~~. The following ~~baseline~~ procedures will be performed:	**the procedures listed below must be performed before the subject re-starts investigational product regardless of the reason for interruption.** The following procedures will be performed t**o reinitiate investigational product**:	for updated Hepatic and Renal monitoring procedures.
Section 8.2.1	Subjects who discontinue investigational product are expected to continue in the study until the end of the study. If a subject experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who discontinue investigational product prior to ~~termination~~ of the study need to also continue to follow the regular visit schedule through ~~to~~ study ~~closure~~. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study ~~termination~~. Early termination procedures should only be conducted if the subject withdraws consent (see Section 9.9.15). • Modification of consent: – Consent may be modified to discontinue study visits but allow ~~semi-annual~~ telephone contact of subject, subject's primary care physician, or personal contacts who can provide information on behalf of the subject by the Investigator – Consent may be modified to discontinue study visits but allow continued access to medical records to assess for ~~suspected~~	Subjects who discontinue investigational product are expected to continue in the study until the end of the study. If a subject experiences a suspected clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the Investigator assesses it as safe. Subjects who discontinue investigational product prior to **completion** of the study need to also continue to follow the regular visit schedule through to study **completion (Month 18 for the Double-Blind Phase or Month 12 for the OLE phase)**. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study **completion**. Early termination procedures should only be conducted if the subject withdraws consent (see Section 9.10.15). • Modification of consent: – Consent may be modified to discontinue study visits but allow **periodic** telephone contact of subject **(in line with the study visit schedule) through completion of the study (Month 18 if initiated in the Double-Blind Phase or Month 12 if initiated in the OLE phase), through the** subject's primary care physician, or	Clarification was added to align Follow-up with visit schedule

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	MACE, and liver-related clinical outcomes	personal contacts who can provide information on behalf of the subject by the Investigator – Consent may be modified to discontinue study visits but allow continued access to medical records **through completion of the study (Month 18 if initiated in the Double-Blind Phase or Month 12 if initiated in the OLE phase)** to assess for **potential** MACE, and liver-related clinical outcomes	
Section 9.3	*New Section*	**9.3. Criteria for Extension of Double-Blind Treatment with Investigational Product** **With the exception of sites in the Ukraine, for subjects who have been unable to complete the liver biopsy procedure at the Month 18 Visit due to the limitations caused by the COVID-19 pandemic and have or will run out of investigational product, investigational product may be extended beyond the Month 18 Visit for a maximum of 3 additional months of the double-blind period. In order for a subject to be eligible for this extension, the following must occur:** **• Assessment of safety laboratory tests (chemistry panel including glucose, hematology panel, coagulation parameters; computed MELD score, and CP score) at Month 18, with review of results by the Medical Monitor and Investigator.** **• Assessment of subject status at the Month 18 Visit must occur, either via an onsite study visit (if possible) or via a telemedicine visit ("virtual**	Guidance to Investigators on acceptable procedures and necessary documentation required during COVID-19 pandemic were added to ensure the safety of the subject in the study as well as the integrity of the study.

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		visit") as an alternative means of enabling Investigators and site staff to evaluate subject status and record any AEs or new medications. At a minimum, these visits must consist of a direct telephone or videocall discussion with the subject by the Investigator or an appropriate designee from the Investigator's team who is currently authorized to undertake examinations on the Investigator's Delegation of Authority Log. If an onsite visit or a telemedicine contact is not feasible (eg, no access to the subject) to assess status, investigational product will not be dispensed. **• If deemed necessary, additional assessment of safety laboratory tests and/or subject status may be performed at the discretion of the Investigator or Medical Monitor. Based on the individual subject-level safety and tolerability assessment, if both the Medical Monitor and the Investigator agree that the benefit-risk profile remains favorable, investigational product may be dispensed, which will provide an additional 3 months of treatment.** **Unless all of the above measures occur, additional investigational product will not be provided.**	
Section 9.4	9.4 Concomitant Medications …	9.4 **Standard of Care and** Concomitant Medications … **If a study subject receives a COVID-19 vaccination, the date(s) of vaccination, vaccine**	Guidance to Investigators on acceptable procedures and necessary documentation required for vaccine information were

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		name, and manufacturer should be recorded as a concomitant medication for each dose (refer to Section 10).	added to ensure the safety of the subject in the study as well as the integrity of the study.
Section 9.4.1	~~Given the prevalence of dyslipidemia in patients with NASH and the potential increase in total and LDL cholesterol following treatment with OCA, it is recommended that Investigators proactively monitor and manage lipid levels via appropriate medicinal interventions.~~ Appendix A provides a general guidance for cholesterol management including monitoring, triggers for intervention, and treatment goals. Use of LDL-lowering medications (eg, simvastatin, atorvastatin, PCSK9 inhibitors) should be at a stable dose ≥30 days before Day 1. During the study, changes to LDL-lowering medication regimen are allowed, given the potential increase in total and LDL cholesterol following treatment with OCA.	Appendix A provides a general guidance for cholesterol management including monitoring, triggers for intervention, and treatment goals. Use of LDL-lowering medications (eg, simvastatin, atorvastatin, PCSK9 inhibitors) should be at a stable dose ≥30 days before Day 1. During the study, changes to LDL-lowering medication regimen are allowed, given the potential increase in total and LDL cholesterol following treatment with OCA.	Introduction language was moved to new Section 9.4.5 so that Section 9.4.1 focuses on lipid lowering medication, as opposed to overall dyslipidemia management (Section 9.4.5)
Section 9.4.3	Subjects taking ~~bile acid sequestrants (~~BAS~~)~~ (including colestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (ie, BAS should be administered 4 hours before or 4 hours after investigational product administration).	**9.3.1. Bile Acid Sequestrants** **Bile acid sequestrants (BAS) have the potential to bind to fat-soluble vitamins, hormones, or medications.** Subjects taking BAS (including colestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of investigational product **in temporal relationship to these agents**, ensuring at least 4 hours between doses of the BAS and/or these antacids and the investigational product (ie, BAS should be	Since the long-term use of BAS can affect the exposure to OCA and its metabolites, guidance was added to encourage Investigators to limit use of longer-term BAS. Other concomitant medications updated to reflect changes in

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	The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine. If ~~clinical~~ indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a biopsy be obtained and sent for central reading.	administered 4 hours before or 4 hours after investigational product administration). **For guidance on using BAS to treat pruritus ≤Grade 2 in severity refer to Section 16.1.6.1.** **Due to the potential of BAS to affect the disposition of OCA, long-term use of BAS should be avoided where possible while taking investigational product. In subjects taking long-term BAS for other medical conditions (eg, hypercholesteremia), other therapies to replace the BAS should be considered.**	progression to cirrhosis and guidance regarding COVID-19 vaccination was added.
Synopsis Section 9.4.5	*New Section and Figure*	**9.4.5. Standard of Care: Management of Dyslipidemia** **Given the prevalence of dyslipidemia in patients with NASH and the potential increase in total cholesterol and LDLc following treatment with OCA, it is recommended that Investigators proactively monitor and manage lipid levels in all subjects as indicated via appropriate medicinal interventions (eg, statins). Recent guidelines stress the importance of evaluating ASCVD risk in all patients to help guide decisions in recommending therapies and reducing LDLc to reduce the risk and prevent onset or recurrence of ASCVD. As such, reducing lipids, particularly LDL, are part of a comprehensive cardiovascular risk reduction strategy. Results from meta-analyses have confirmed the dose-dependent reduction in ASCVD with LDLc-lowering agents; the greater the absolute LDLc reduction,**	Guidance on the management of dyslipidemia according to current guidelines (ACC/AHA/ESC/EAS) and based on ASCVD risk was added to optimize and proactively manage subjects based on cardiovascular risk factors before and when LDLc elevations occur. Existing bullet was removed

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		the greater the CV risk reduction. Recent guidelines for the management of lipids, such as the 2019 ESC/EAS Guidelines (Mach 2020), suggest that LDLc targets should be individualized based on available treatments and each subject's overall ASCVD risk profile. The targeted approach to lipid management is aimed at reducing atherosclerotic risk by substantially lowering LDLc to levels that have been achieved in recent large-scale trials (Figure 4).	
Section 9.4.6	*New Section*	**9.4.6. Standard of Care: Management of Hyperglycemia** **Subjects with type 2 diabetes mellitus and those who are at risk for developing hyperglycemia should be closely monitored throughout the study in order to ensure appropriate therapeutic interventions based on current guidelines to mitigate potential elevations of serum glucose and initiate them when indicated. The Investigator should proactively consider major risk factors for developing hyperglycemia that include family history of type 2 diabetes; obesity; African American, Native American, Hispanic or Asian American heritage; hypertension; dyslipidemia, or history of gestational diabetes. Early signs and symptoms of hyperglycemia that include polyuria, polydipsia, polyphagia, blurred vision, fatigue and headaches should also be monitored.** **Subjects who experience treatment-emergent hyperglycemia should be closely monitored and treatment should be based on current guidelines.**	Guidance on the management of hyperglycemia according to current guidelines (ADA and EASD) was added to optimize and proactively manage subjects before elevations occur Additional language referring subjects to their treating physician and/or endocrinologist was added for subjects who develop hyperglycemia

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		Initiation of therapy should take into consideration each subject's underlying health status and the use of appropriate glycemic targets. **The management of hyperglycemia depends on several factors including: the duration, frequency, and severity of hyperglycemia, and the subject's age, health, and cognitive function. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have updated their recommendations on the management of hyperglycemia based on underlying risk factors including underlying cardiovascular and renal disease. According to these guidelines, glycemic treatment targets should be individualized based on patient preferences and goals, risk of adverse effects of therapy (eg, hypoglycemia and weight gain), and subject characteristics, including frailty and comorbid conditions (Davies 2018). Glycemic management is primarily assessed by measuring HbA1c and the choice of glucose-lowering medications should be accompanied by lifestyle management, weight loss, exercise, dietary modification, diabetes self-management education and support, and patient-centered care.** **While criteria for initiating therapy requires individualizing HbA1c targets, a reasonable HbA1c target is approximately ≤7% (53 mmol/mol) (Davies 2018). The selection of the appropriate individualized therapy is**	

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		described in current guidelines from ADA and EASD for management of hyperglycemia (Appendix B). **Subjects displaying increasing fasting glucose, HBA1c, or HOMA-IR levels should be referred to either their treating physician, if already under care for diabetes, or to their HCP or an endocrinologist if they experience new onset type 2 diabetes mellitus.** Reference: **Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes care. 2018 Dec;41(12):2669-701.**	
Section 9.10.4 through Section 9.10.15	• Assess and record any pretreatment AEs • Assess signs and symptoms of ~~h~~epatic injury or decompensation • Verify inclusion and exclusion criteria for eligibility	• Assess and record any **TE**AEs • Assess signs and symptoms of: – **H**epatic injury or decompensation – **Intercurrent illness and/or potential adverse events (Appendix C)**	Assessment of intercurrent illness at each study visit was added to reflect increased subject education and monitoring
Section 9.10.10	9.10.10.DB Month 18/EOT/EOS/OLE Day 1 Visit for Subjects Continuing into the OLE All Month 18/EOT/EOS procedures, except for the post-dose collection of blood samples for subjects participating in the PK and/or	9.10.10.DB Month 18/EOT/EOS/OLE Day 1 Visit for Subjects Continuing into the OLE **For subjects who are unable to complete the liver biopsy procedure at the Month 18 Visit due to the limitations caused by the COVID-19 pandemic and have or will run out of**	Guidance to Investigators on acceptable procedures and necessary documentation required during COVID-19 pandemic

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	[redacted] Liver biopsy (must be completed prior to dosing with investigational product at Day 1 OLE). ~~If the~~ subject complete~~d~~ a liver biopsy as part of the EOT visit, and remains in the study, a biopsy is not required at the Month 18 visit.	**investigational product, investigational product may be extended beyond the Month 18 Visit for a maximum of 3 additional months of the double-blind period (refer to Section 9.3 for requirements of this extension). Regardless of whether these subjects are eligible for the additional supply of investigational product, they are to return to the site for an unscheduled visit to complete the liver biopsy (and other procedures assessments as required) as soon as practical following lifting/easing of the COVID-19 restrictions (refer to Section 9.10.16 for details of this visit).** All Month 18/EOT/EOS procedures, except for the post-dose collection of blood samples for subjects participating in the PK and/or [redacted], should be done before dosing, including trough PK sampling. … Liver biopsy (must be completed prior to dosing with investigational product at Day 1 OLE). **When a** subject completes a liver biopsy as part of the EOT visit **during the Double-Blind Phase**, and remains in the study, a **second** biopsy is not required at the Month 18 Visit. **Refer to Section 9.10.16 for guidance for subjects unable to complete the Month 18 biopsy due to COVID-19 restrictions.**	were added to ensure the safety of the subject in the study as well as the integrity of the study.
Section 9.10.10.1	Subjects who continue into the OLE Phase after completing the procedures listed for the Month 18 Visit (Section 9.10.10) will undergo the following procedures:	Subjects who continue into the OLE Phase after completing the procedures listed for the Month 18 Visit (Section 9.10.10) will undergo the following procedures:	Guidance provided to clarify how early subjects may sign the ICF for the OLE

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	• Review OLE ICF and obtain signatures before performing any OLE-specific procedures	• Review OLE ICF and obtain signatures before performing any OLE-specific procedures. **The OLE ICF may be obtained as early as the Month 15 study visit in the Double-Blind Phase.**	
Section 9.10.13	• Calculations will be performed by the Sponsor or designee for: – MELD Score – CP Score/Class (assessment of ascites and hepatic encephalopathy is required) – Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI) – Noninvasive panel of liver fibrosis (ELF and Fibrometer) – ~~Suspected~~ DILI management algorithm (liver biochemistry) • Perform a urine-based β-hCG pregnancy test for females of childbearing potential	Calculations will be performed by the Sponsor or designee for: – MELD Score – CP Score/Class (assessment of ascites and hepatic encephalopathy is required) – Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI) – Noninvasive panel of liver fibrosis (ELF and Fibrometer) – **Potential** DILI management algorithm (liver biochemistry) • **Obtain urine sample for urinalysis** • Perform a urine-based β-hCG pregnancy test for females of childbearing potential	Frequency of urinalysis updated to reflect changes to renal monitoring
Section 9.10.16	The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. As appropriate, the Medical Monitor should be contacted.	The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. As appropriate, the Medical Monitor should be contacted. **Additionally, all subjects who were unable to complete the liver biopsy at the Month 18 Visit due to the restrictions from the COVID-19 pandemic, regardless of whether they received additional supply of investigational product or not as described in Section 9.3, are to return to**	Guidance to Investigators on collecting the Month 18 liver biopsy during the COVID-19 pandemic a were added to ensure the safety of the subject in the study as well as the integrity of the study.

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		the site for an unscheduled visit to complete the liver biopsy as soon as practical following lifting/easing of the COVID-19 restrictions. At this unscheduled visit, the types of procedures/assessments required to be performed, in addition to the liver biopsy, are the following: **• If this unscheduled visit occurs more than 6 weeks since the original Month 18 Visit, then all Month 18 study visit procedures are to be performed, including but not limited to procedures that could not be performed at Month 18 due to COVID-19 restrictions.** **• If this unscheduled visit occurs within 6 weeks since the original Month 18 Visit, then only the assessments that could not be obtained at the Month 18 Visit and recording of any AEs and concomitant medications are to be completed.** **• In addition, for any subject who wishes to enroll in the OLE phase, safety laboratory tests (refer to Table 2) as well as any additional assessments required to determine eligibility for the OLE (including EGD) are to be completed.**	
Section 10	*New Section.*	**STUDY MANAGEMENT DURING COVID-19** **The COVID-19 infection control measures that have been imposed by local and national governments to contain the COVID-19 pandemic have resulted in some study sites not being able to perform protocol-specified procedures and assessments such as collecting laboratory samples. In addition, some subjects are unable**	Guidance to Investigators on acceptable procedures and necessary documentation required during COVID-19 pandemic and vaccine information were added to ensure the

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		to return to study sites for evaluations and/or to receive continued supply of investigational product. Enforcement of many restrictions by local authorities have also affected the site monitor's ability to perform on-site monitoring during the pandemic. **This section describes the processes under which subjects who are unable or unwilling to return to study sites may complete protocol-specified assessments and continue to receive investigational product until in-person site visits can resume. To ensure the continued safety monitoring of the participating subject and to minimize the potential adverse impact on achieving the objectives of the study due to the restrictions from the COVID-19 pandemic, the following approaches may be applied to the study protocol. Investigators should document the reason for any contingency measures implemented and how restrictions related to COVID-19 led to the changes in study conduct, duration of those changes, and how those study participants were impacted.** **Alternative Approaches for Study Conduct Due to COVID-19** **For subjects who are unable to attend in-person study visits due to national or local restrictions, the following alternative options are deemed acceptable, upon required Ethic Committee or Regulatory Agency approval, to satisfy the requirements for continued supply of investigational product:**	safety of the subject in the study as well as the integrity of the study.

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

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		▪ **Liver safety labs: Direct and Total bilirubin; AST, ALT, ALP, GGT, INR, platelet count, sodium, albumin and creatinine.** ▪ **Non-Liver safety labs: CBC & Diff; standard electrolytes (sodium & potassium only), lipid panel, fasting blood glucose, and urine-based β-hCG pregnancy test.** • **Investigational Product Distribution: Investigational product may be sent directly to the subject from either the study site or a third-party vendor via a courier service if subjects are not able to attend study site visits. Direct shipment of investigational product from the Investigator site to subjects must adhere to the site's institutional and pharmacy procedures and country specific requirements. If the Investigator is unable to evaluate safety and tolerability and assess the benefit-risk for the individual subject, the subject must interrupt investigational product until the assessment can be completed.** • **Home Visits: If laboratory tests cannot be obtained from local laboratories, qualified home nursing support (where available and permitted) is an accepted option that may be employed to supplement telemedicine interactions to enable for the collection and processing of blood samples for laboratory tests including PK and PD samples, if**	

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		required, and conduct other limited assessments (eg, assessment of vital signs, completion of protocol required subject questionnaires). • **Monitoring: Cancelling or postponing of on-site monitoring visits and extension of the period between monitoring visits may occur per specific local guidelines and regulations. Alternatively, additional off-site monitoring activities such as phone calls, video visits, emails may be used to discuss the trial with the Investigator and site staff. Remote source verification also may be performed if it is permissible by the local regulations.** **Any other alternative procedures or assessments not listed above must be discussed with the Medical Monitor and documented by the Investigator, maintain subject participant confidentiality and be compliant with HIPPA/GDPR and 21 CFR Part 11 guidance.** **In addition to regularly collected trial data, available COVID-19 related data such as COVID-19 testing will also be collected for all subjects. Any subject that contracts the SARS-CoV-2 virus should have this reported as an adverse event under the description "COVID-19" per MedDRA 23.1. If a subject is hospitalized for COVID-19 complications an SAE should be reported in accordance with the protocol and national requirements.** **COVID-19 Vaccine**	

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		COVID-19 vaccination (with vaccines approved for emergency use in the country where you practice) is allowable for participants enrolled in Intercept-sponsored PBC and NASH clinical trials. Of note, as the currently approved COVID-19 vaccines have not been specifically tested in the NASH or PBC subject population, nor in the pediatric population suffering from biliary atresia (BA), there are no safety data available specific to the use of COVID-19 vaccines in PBC subjects, NASH subjects, or in children suffering from BA. **If a subject receives a COVID-19 vaccination, the date(s) of vaccination(s), vaccine name, and manufacturer should be recorded as a concomitant medication for each dose.**	
Synopsis Section 13.1.1	~~In addition to the primary scoring using NASH CRN, biopsy samples will also be scored based on the modified Ishak criteria (Ishak 1995), Laennec staging (Wang 2015), and SAF scoring (Bedossa 2014), and for quantitative collagen.~~	[redacted]	The updated independent consensus read method will only use the NASH CRN scoring criteria to assess biopsy samples
Section 14	14.CLINICAL PHARMACOLOGY ASSESSMENTS Subjects who receive at least one dose of OCA and have measurable plasma PK concentration data available will be included in the PK analysis	14.CLINICAL PHARMACOLOGY ASSESSMENTS Subjects who receive at least one dose of OCA and have measurable plasma PK concentration data available will be included in the PK analysis. **A PK blood sample should be collected in subjects who experience a SAE during the study. Blood samples should be collected as soon as possible after the SAE is identified but no later**	Recommendation to collect a PK sample within 7 days of an SAE was added to better characterize the exposure-response relationship for safety.

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		than 7 days after the onset of the SAE. The times of the last dose of investigational product, the last meal, and the PK sample collection should be recorded. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.	
Section 15.1.1.1	Subjects should be instructed to contact the site promptly if they develop signs and symptoms of ~~suspected 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 the whites of eyes, and bruising easily.~~	Subjects should be instructed to contact the site promptly if they develop **any of the** signs and symptoms of **intercurrent illness and/or potential adverse events listed in Appendix C**.	Symptoms updated to reflect changes in Appendix C for monitoring and education
Section 16.1.1.3	An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: • Death • Is ~~immediately~~ life threatening • Requires in-subject hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability or incapacity • Results in a congenital abnormality or birth defect • Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above	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 life threatening • Requires in-subject hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability or incapacity • Results in a congenital abnormality or birth defect • Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above	Removal of immediately, as any life threatening event is considered serious Recommendation to collect a PK sample within 7 days of an SAE was added to better characterize the exposure-response relationship for safety.

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	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	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 **A PK blood sample should be collected in subjects who experience a serious adverse event during the study. Blood samples should be collected as soon as possible after the serious adverse event is identified but no later than 7 days after the onset of the serious adverse event. The times of the last dose of investigational product, the last meal, and the PK sample collection will be recorded in the eCRF. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.**	
Section 16.1.6.1	• Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the eCRF. Per Section 7.7, subjects with pruritus ≥Grade 3 in severity (per CTCAE) ~~and possibly, probably, or definitely related to investigational product~~ must discontinue investigational product but are encouraged to continue study visits.	• Drug holiday: A drug holiday is defined as an Investigator 'prescribed' complete interruption of dosing for 1 or more consecutive days (ie, non-daily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the eCRF. Per Section 7.7, subjects with pruritus ≥Grade 3 in severity (per CTCAE) must discontinue investigational product but are encouraged to continue study visits. • • **Short-term use of** BAS:	Relation to IP was removed to align with Section 7.7. If pruritus ≥Grade 3 in severity is experienced IP should be discontinued Since the long-term use of BAS can affect the exposure to OCA, guidance was added to

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	• ~~Prescribing~~ BAS ~~(see Section 9.3.3): Subjects taking BAS (including colestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) should be instructed to stagger their dosing of investigational product, ensuring at least 4 hours between doses of the BAS and investigational product~~. • Other therapies may be ~~tried~~ as deemed clinically appropriate.	**- Use of BAS may be considered in conjunction with a change in investigational product dosing frequency (ie, every other day dosing) for approximately 2 weeks. The subject should be evaluated after the 2-week intervention to assess the status of pruritus and stop the use of BAS as deemed appropriate by the Investigator. If the Investigator considers that the subject can tolerate investigational product, daily dosing may be reinitiated.** **- If the subject cannot tolerate investigational product after stopping BAS due to ongoing pruritus, the Investigator should consult with the Medical Monitor to determine a treatment plan. This may include continuing every other day dosing, interrupting or discontinuing investigational product.** **- If after 4 to 6 weeks (or up to 3 courses of a 2-week BAS therapy), the subject is unable to tolerate investigational product without BAS treatment, the Investigator should consider, in consultation with the Medical Monitor, discontinuing investigational product.** **- The subject should make every effort to avoid long-term use of BAS for pruritus while taking investigational product. For additional guidance on BAS refer to Section 9.4.3**	encourage Investigators to limit the use of BAS to 2 weeks at a time and possible rechallenge of OCA. Additional guidance was provided on when IP discontinuation should be considered

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		• Other **medical** therapies **for the management of pruritus** may be **considered** as deemed clinically appropriate **and based on current practice guidelines (EASL 2017) or literature (Hegade 2015).** **References:** **European Association for the Study of the Liver (EASL). EASL clinical practice guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–72.** **Hegade VS, Kendrick SF, Jones DE. Drug treatment of pruritus in liver diseases. Clin Med. 2015 Aug;15(4):351-7.**	
Section 16.1.12	If a subject experiences symptoms consistent with cholelithiasis or pancreatitis, the subject should ~~undergo~~ a complete evaluation for both conditions consistent with local standards of care. If symptomatic cholelithiasis and/or cholecystitis is diagnosed~~, investigational product should be interrupted, and~~ the subject should be managed and monitored as described in Section 7.5.1.	If a subject experiences symptoms consistent with **symptomatic** cholelithiasis **and/or complications related to gallstone disease** or pancreatitis, the subject should **have investigational product interrupted while undergoing** a complete evaluation for both conditions consistent with local standards of care. If symptomatic cholelithiasis and/or cholecystitis is diagnosed the subject should be managed and monitored as described in Section 7.5.1.	Updated to reflect changes in guidance for cholelithiasis and/or cholecystitis (section 7.5.1)
Section 16.2.7	Blood and urine samples for laboratory assessments will be collected at the visits specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase). Full instructions	Blood and urine samples for laboratory assessments will be collected at the visits specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase). Full instructions concerning the number and type of	Section updated to provide clarification on use of local lab and inclusion or

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	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 a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit. All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary.	samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in a separate procedural manual. All necessary collection supplies will be provided by the central laboratory and will be appropriately assembled for the specific evaluations required at each visit. **If 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 laboratory is required. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges. All local laboratory data, including the reference ranges, are to be collected and entered in the eCRF within 2 days of receiving the results. For guidance on alternative processes under which subjects may complete the protocol-specified assessments under COVID-19 restrictions refer to Section 10.** All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product related AE, is identified; or until further follow-up is deemed medically unnecessary. **The Investigator should proactively monitor and manage lipid levels in all subjects as indicated via appropriate medical interventions (eg, statins). Recent guidelines stress the importance of evaluating ASCVD risk in all subjects to help**	results/reference ranges into the eCRF Monitoring of lipids language updated to reflect changes in Section 9.3.3

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		guide decisions in recommending therapies and reducing LDLc to reduce the risk and prevent onset or recurrence of ASCVD (refer to Section 9.4.5 and Appendix A.	
Section 16.2.7, Table 13	*Table updated to include calculation of eGFR added for clarity based off updated renal monitoring.*		
Section 16.2.8	16.2.8. Pruritus Assessment Pruritus Visual Analog Scale (VAS): The pruritus VAS will be used to assess a subject's experience and severity of pruritus.	16.2.8. Pruritus Assessment Pruritus Visual Analog Scale (VAS): The pruritus VAS will be used to assess a subject's experience and severity of pruritus. **This assessment should be captured on the blue pad.**	Clarification added for Investigators on how to document pruritus assessment.
Section 17.1	…	**…** **Additional analysis population (if any) will be specified in the SAP.**	Note added to analysis populations to specify additional details will be specified in the SAP.
Section 17.3	17.3. Primary Efficacy Analysis The primary efficacy analysis will be conducted using the ITT population and test the following hypotheses: • H01: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to ~~Month 18~~ is equal between placebo and OCA 10 to 25 mg titration. • H11: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular	17.3. Primary Efficacy Analysis The primary efficacy analysis will be conducted using the ITT population and test the following hypotheses: • H01: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to **the end of the Double-Blind Phase** is equal between placebo and OCA 10 to 25 mg titration. • H11: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH	"Month 18" was replaced with "end of double-blind phase" to reflect biopsies that may have occurred at Month 12 (through protocol version 4) and Month 18

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	inflammation using the NASH CRN scoring system, from Baseline to ~~Month 18~~ is different between placebo and OCA 10 to 25 mg titration. • H02: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to ~~Month 18~~ is equal between placebo and OCA 10 mg. • H12: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to ~~Month 18~~ is different between placebo and OCA 10 mg. The type I error for primary efficacy analysis will be controlled at 0.05. For the comparison of the primary efficacy endpoint, a Cochran Mantel Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] will be ~~used~~. ~~Missing values will be considered a nonresponse.~~ ~~Exploratory~~ analyses of the primary endpoint will be conducted using the mITT and PP populations.	CRN scoring system, from Baseline to **the end of the Double-Blind Phase** is different between placebo and OCA 10 to 25 mg titration. • H02: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to **the end of the Double-Blind Phase** is equal between placebo and OCA 10 mg. • H12: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation using the NASH CRN scoring system, from Baseline to **the end of the Double-Blind Phase** is different between placebo and OCA 10 mg. The **overall** type I error for primary efficacy analysis will be controlled at 0.05. **The primary analysis between placebo and OCA 10 to 25 mg titration will be tested first at 5% alpha and the hypothesis (H02) between placebo and OCA 10 mg will be tested if the null hypothesis (H01) between placebo and OCA 10 to 25 mg titration is rejected at 5% level.** For the comparison of the primary efficacy endpoint, a Cochran Mantel Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] will be **performed**. **Additional details regarding**	

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		analyses with missing values will be provided in the SAP. Analyses of the primary endpoint will be conducted using the mITT and PP populations **and a sensitivity analysis will be conducted in the Month 18 biopsy-only population.**	
Section 17.4 Section 17.5	17.4. Secondary Efficacy Analyses ~~The key secondary efficacy analyses will be conducted using the ITT population.~~ ~~The key secondary efficacy endpoint is:~~ ~~• Percentage of subjects with fibrosis improvement by at least 2 stages using Ishak scoring criteria from Baseline to Month 18~~ ~~The percentage of subjects with fibrosis improvement by at least 2 stages using Ishak scoring criteria will be analyzed similarly to the primary endpoint.~~ ~~The hypothesis testing of the key secondary endpoint will be conducted in a sequential closed testing gate-keeping procedure, provided the primary efficacy comparison is statistically significant in favor of OCA. If the primary efficacy comparison is not statistically significant, then the comparison of key secondary efficacy endpoint will be considered descriptive and exploratory.~~ ~~Additional secondary endpoints will be analyzed; however, statistical testing will be considered descriptive and exploratory only.~~ ~~17.5. Additional Secondary Efficacy Analyses~~	17.4. Secondary Efficacy Analyses **Secondary** efficacy analyses will be conducted using mITT and PP populations. 17.4.1. Histology Endpoints The following **secondary efficacy** endpoints will be analyzed: • Percentage of subjects with resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" as characterized/quantified by a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, at **the end of the Double-Blind Phase**. • Percentage of subjects with resolution of NASH based on **pathologist's** overall interpretation **of the presence or absence of definite NASH at the end of the Double-Blind Phase**. • Histological changes in fibrosis status including: (1) improvement, or (2) no **change**, from Baseline to the **end of the Double-Blind Phase** using the NASH CRN scoring system • Percentage of subjects with improvement in each component of NAS (steatosis, lobular inflammation,	Secondary and Exploratory objectives were reorganized to more accurately capture analyses. "Month 18" was replaced with "end of double-blind phase" to reflect biopsies that may have occurred at Month 12 (through protocol version 4) and Month 18 Histology objectives were updated to reflect new central histology method, which will only include NASH CRN scoring.

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	~~Additional~~ efficacy analyses will be conducted using mITT and PP populations. ~~Statistical testing for additional secondary endpoints will be considered descriptive and exploratory only.~~ 17.5.1. ~~Other~~ Histology Endpoints The following ~~additional~~ endpoints will be analyzed: • ~~Percentage of subjects with changes in fibrosis using the following criteria:~~ ~~o NASH CRN scoring system from Baseline to Month 18~~ ~~o At least 2-stage improvement~~ • ~~Ishak scoring criteria from Baseline to Month 18~~ ~~o At least 1-stage improvement~~ ~~o Improvement to Stage 4 or lower~~ • ~~Laennec staging system from Baseline to Month 18~~ ~~o At least 1-point improvement~~ ~~o Improvement to Stage 3 or lower~~ • ~~Percentage of subjects with no worsening (includes improvement) of fibrosis using the following criteria:~~ ~~o Ishak scoring criteria (if baseline Ishak stage <6) from Baseline to Month 18~~ ~~o Laennec staging system (if baseline Laennec stage <4C) from Baseline to Month 18~~	and hepatocellular ballooning) from Baseline t**o the end of the Double-Blind Phase** Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no]). Overall shift and frequency tables will be presented for NAS score, NAS components, SAF score, and fibrosis scores (according to NASH CRN criteria). 17.4.2. Clinical Outcomes Analyses of the clinical outcomes composite endpoint, individual components of outcome events, and occurrence of HCC will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo. Treatment groups will be compared on the percentage of subjects who reported any of the following adjudicated events, as well as the time to first occurrence: • Death (all cause) • MELD score ≥15 • Liver transplant • Worsening of CP score by at least 2 points • Hospitalization (as defined by a stay of ≥24 hours) for onset of: • Variceal bleed • Hepatic encephalopathy (as defined by a West Haven score of ≥2) • Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)	

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	~~• Percentage of subjects with progression of fibrosis using the following criteria:~~ ~~o Ishak scoring criteria (if baseline Ishak stage <6) from Baseline to Month 18~~ ~~o Laennec staging system (if baseline Laennec stage <4C) from Baseline to Month 18~~ • ~~Changes in fibrosis score from Baseline to Month 18~~ • Percentage of subjects with resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" as characterized/quantified by a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, at ~~Month 18~~. • Percentage of subjects with resolution of NASH based on overall ~~pathologist~~ interpretation ~~(resolution of definite NASH)~~ at ~~Month 18~~. • Change in morphometric assessment of quantitative collagen from Baseline to ~~Month 18~~ (assessed as PCA) *[moved to exploratory]* • Percentage of subjects with improvement in each component of NAS (steatosis, lobular inflammation, and hepatocellular ballooning) from Baseline to ~~Month 18~~ *[moved to exploratory]* • Changes in NAS from Baseline to ~~Month 18~~ *[moved to exploratory]*	• Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) • HCC (as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy) will be analyzed as a separate outcome event. Only adjudicated events will be included in analyses. Subjects with none of these events will be censored at the date of last contact. For the analysis of time to first occurrence of adjudicated events, a log rank test stratified by the randomization stratification factor **(presence of type 2 diabetes at enrollment [yes/no])** will be used. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians and corresponding 95% confidence intervals (CIs), if the medians can be estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. Subjects without any documentation of events will be censored at the date of last contact by the **end of the Double-Blind Phase**. In addition, treatment groups will be compared on each component of the outcome events. The percentage of subjects who reported any adjudicated events will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no]). Percentage of subjects who reported each	

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	~~• Changes in SAF score from Baseline to Month 18~~ Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no]). ~~The change in NAS, SAF, and [redacted] will be analyzed using an analysis of covariance (ANCOVA) model at each visit with change from baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and baseline as a covariate. In addition, changes in NAS and SAF score will be summarized by each category.~~ Overall shift and frequency tables will be presented for ~~NAS score,~~ NAS components~~, SAF score~~, and fibrosis scores (according to NASH CRN~~, Ishak, and Laennec~~ criteria). 17.5.2. Clinical Outcomes Analyses of the clinical outcomes composite endpoint, ~~individual components of outcome events,~~ and occurrence of HCC will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo. Treatment groups will be compared on the percentage of subjects who reported any of the following adjudicated events, as well as the time to first occurrence: • Death (all cause) • MELD score ≥15 • Liver transplant • Worsening of CP score by at least 2 points	component of the outcome events will also be analyzed separately in a similar manner. [redacted]	

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	• Hospitalization (as defined by a stay of ≥24 hours) for onset of: o Variceal bleed o Hepatic encephalopathy (as defined by a West Haven score of ≥2) o Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) ~~The time to occurrence of~~ HCC (as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy) will be analyzed as a separate outcome event. Only adjudicated events will be included in analyses. Subjects with none of these events will be censored at the date of last contact. For the analysis of time to first occurrence of adjudicated events, a log rank test stratified by the randomization stratification factor will be used. Kaplan-Meier (KM) estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM estimate of the medians and corresponding 95% confidence intervals (CIs), if the medians can be estimated. The number and percent of subjects censored and with events will be presented. The hazard ratio and 95% CI will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect. Subjects without any	[redacted] … 17.5.6. **Disease Progression as Assessed by MELD Score** Hepatic function using MELD score will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit.	

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	documentation of events will be censored at the date of last contact. In addition, treatment groups will be compared on each component of the outcome events. The percentage of subjects who reported any adjudicated events will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no]). Percentage of subjects who reported each component of the outcome events will also be analyzed separately in a similar manner. … 17.5.6. ~~Hepatic Function~~ Hepatic function using MELD ~~and CP~~ score~~s~~ will be summarized by treatment group using descriptive statistics at baseline and at each post-baseline visit.		
Section 17.9.3	For the analyses ~~of the primary and key secondary histological efficacy endpoints,~~ in which subjects are classified as either a responder or a non-responder (binary outcome), any subject who does not provide an assessment at the specified timepoint for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator. An "observed cases" analyses will also be conducted, excluding those subjects who do not provide an assessment at the specified timepoint	For the **primary** analyses in which subjects are classified as either a responder or a non-responder (binary outcome), any subject who does not provide an assessment at the specified timepoint for the defining of response will be considered to be a non-responder. That is, for the percentage of responders, the subject will be included in the denominator and will not contribute to the numerator. **Additional details regarding the secondary histological endpoints are provided in the SAP.** An "observed cases" analyses will also be conducted **as sensitivity analyses**, excluding those subjects who do not provide an assessment at the specified timepoint for the defining of response.	Language updated to reflect removal of key secondary objective; responder classification will be applied to all applicable secondary objectives

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	for the defining of response. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.	That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.	
Section 17.10	The primary and ~~key~~ secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) using the ITT population. Subgroups will be assessed at Baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group). Baseline subgroups of interest include, but are not limited to: age, sex, race, BMI, baseline diabetes, baseline fibrosis stage, FRS, statin or antihypertensive medication use at Baseline, baseline ALT, AST, GGT, and geographic region.	The primary and secondary efficacy endpoints will be analyzed for subject subgroups (eg, age, sex, and race) using the ITT population. Subgroups will be assessed at Baseline and only if there are a sufficient number of subjects in each group (eg, >5 subjects per group). Baseline subgroups of interest include, but are not limited to: age, sex, race, BMI, baseline diabetes, baseline fibrosis stage, FRS, statin or antihypertensive medication use at Baseline, baseline ALT, AST, GGT, and geographic region. **Additional details will be provided in the SAP**.	Language updated to reflect removal of key secondary objective. Subgroups will be applied to all secondary objectives
Synopsis Section 17.11	Safety evaluations will comprise treatment-emergent AEs, AEs of special interest including pruritus ~~and hepatic safety,~~ adjudicated CV events, vital signs, electrocardiograms (ECGs), pruritus VAS, and clinical laboratory results.	Safety evaluations will comprise treatment-emergent AEs, AEs of special interest **(**including **cardiovascular**, pruritus, **renal, urinary tracts stones including nephrolithiasis, gallbladder/gallstone-related, pancreatitis, hepatic, dyslipidemia and hyperglycemia/new-onset diabetes mellitus AEs)**, adjudicated CV events, **adjudicated AKI events, adjudicated events of hepatic injury**, vital signs, electrocardiograms (ECGs), pruritus VAS, and clinical laboratory results.	Updated to include additional adjudication committees and clarification on AESIs.
Section 17.11.2	*New Section*	**17.11.1.Hepatic and Renal Safety Adjudication** **Potential events of hepatic injury and AKI will be adjudicated during the study (Section 17.14). The adjudication of the events of hepatic injury**	Section added to reflect additional adjudication committees.

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		will be separate from the adjudication of events for the assessment of outcomes in this study. The adjudication of potential events of hepatic injury and AKI will be further defined in the HSAC charter and the Renal Adjudication Committee charter, respectively.	
Section 17.11.3	17.11.3.~~Adjudicated~~ Cardiovascular Events Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure). Other events potentially related to adverse cardiovascular outcomes are defined in Appendix E and will be included in the Cardiovascular Adjudication Committee Charter for adjudication. … The time-to-event endpoints include:	17.11.3.Cardiovascular Events **Adjudication** Adjudicated cardiovascular events include core MACE (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and expanded MACE (unstable angina requiring hospitalization, transient ischemic attack, peripheral or coronary revascularization procedures, hospitalization for congestive heart failure **and arrhythmias). Any hospitalization (≥24 hours) where a cause has not been identified by the Investigator will be treated as a cardiovascular event and sent for adjudication.** Other events potentially related to adverse cardiovascular outcomes are defined in Appendix E and will be included in the Cardiovascular Adjudication Committee Charter for adjudication. … The time-to-event endpoints include: **• Time from randomization to the first occurrence of arrhythmia**	Definition of CV events for adjudication was updated to be consistent with the criteria defined in the CAC charter.
Synopsis Section 17.12.2	*New Section*	**17.12.2.Efficacy Analyses (OLE)** **The occurrence of all-cause mortality and liver-related clinical outcomes will be summarized.**	Efficacy analyses occurring in the OLE was added to reflect additional objectives specified.

Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
		For additional efficacy analysis, please refer to SAP for more details.	
Section 17.13	The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review PK, safety and efficacy data as well as the adjudication assessments from the ~~2~~ adjudication committees listed in Section 17.14. 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. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked. ~~Data listings provided to the DMC do not contain individual subject treatment information; however, the DMC will have access to the database and may unblind individual subject data as appropriate.~~ Summary tables reviewed by the DMC during closed sessions will include an overall column containing information regarding all subjects and separate treatment columns with fake labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including	The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review PK, safety and efficacy data as well as the adjudication assessments from the **4** adjudication committees listed in Section 17.14. 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. The closed minutes will be made available to the appointed Sponsor representatives only after the database is locked. Summary tables reviewed by the DMC during closed sessions will **be unblinded and** include an overall column containing information regarding all subjects and separate treatment columns with fake labels, ie, the actual treatment groups are used, but are not identified. Data reviewed during the meetings will include, at a minimum, disposition, demographics, exposure, clinical laboratory results, MedDRA coded AEs, and AEs leading to early withdrawal of investigational product. At each meeting, detailed narratives of interval SAEs (including events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs. **In addition, specific summary data focused on hepatic and renal safety are reviewed by the DMC, including an aggregate unblinded summary of adjudicated cases of suspected**	DMC responsibilities expanded to include review of aggregate analyses for all adjudication committees.

Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
	events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.	**hepatic injury and AKI, provided on a quarterly basis or ad hoc as appropriate.**	
Synopsis, Section 17.14	~~Suspected~~ liver-related clinical outcomes, ~~and~~ MACE ~~and drug-related hepatic injury events~~ that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The ~~2~~ committees and event types they are responsible for adjudicating are as follows: • Cardiovascular Adjudication Committee: Adjudicates all ~~suspected~~ MACE, including all deaths • Hepatic Outcomes Committee: Adjudicates all deaths and ~~suspected~~ liver-related clinical outcomes Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the ~~suspected~~ 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. 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. Specific details of the events that will be adjudicated by the Cardiovascular Adjudication	**Potential** liver-related clinical outcomes **and potential events of hepatic injury, AKI**, MACE, **deaths, and hospitalizations (depending on the cause)** that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The **4** committees and event types they are responsible for adjudicating are as follows: • Cardiovascular Adjudication Committee: Adjudicates all **potential** MACE, (including all deaths) **and hospitalizations (depending on the cause)** • Hepatic Outcomes Committee: Adjudicates all deaths and **potential** liver-related clinical outcomes **• HSAC: Adjudicates all events of potential hepatic injury** **• Renal Adjudication Committee: Adjudicates all potential events of AKI** Each adjudication committee will have 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. The adjudication committee members will include experts with relevant adjudication experience; they	Section updated to reflect initiation of renal and hepatic injury adjudication committees. Clarification added to CAC and Hepatic Outcomes Committee to more accurately define events that are being sent for adjudication per the charter. Clarification added to confirm no protected health information will be provided to the adjudication committees.

Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
	Committee ~~and~~ Hepatic Outcomes Committee 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 Any candidate found to have a conflict or whose name is listed on the FDA debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest, they will be replaced. The adjudication of ~~suspected~~ events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual subject treatment or site-specific information. 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.	will not be involved in the study as Investigators, DMC members, or consultants. Specific details of the events that will be adjudicated by the Cardiovascular Adjudication Committee, Hepatic Outcomes Committee, **HSAC, and the Renal Adjudication Committee** 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 Any candidate found to have a conflict or whose name is listed on the FDA debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest, they will be replaced. The adjudication of **potential** events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual subject treatment or site-specific information. **All protected health information will remain confidential and will not be available to the adjudication committee.** The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.	
Appendix A	This guidance summarizes recommendations for the management of LDL cholesterol based on the	This guidance summarizes recommendations for the management of LDL cholesterol based on the	Appendix was reviewed and

Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
	ACC/AHA ~~2013~~ Guideline on the ~~Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (Ray 2014)~~ and the European ~~Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Perk 2012)~~.	ACC/AHA **2019** Guideline on the **Primary Prevention of Cardiovascular Disease** (**Arnett 2019**) and the European **Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk (Mach 2020)**. References: **Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep;140(11):e596-e646.** **Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal. 2020 Jan;41(1):111-88.**	updated based on more recent US and European guidelines.
Appendix B	*New Appendix.* *Inclusion of management of hyperglycemia appendix as a guidance to Investigators on the appropriate therapy be current guidelines.* Reference:		

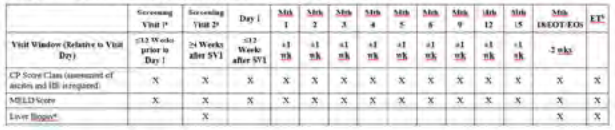
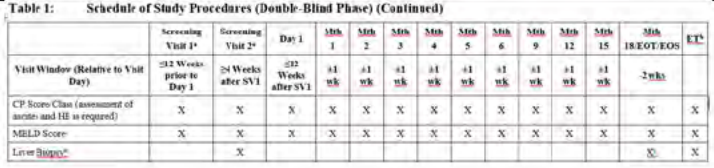
Section	Original Text (Version 6.0, 06 Mar 2020)	Revised Text (Version 7.0, 16 Jun 2021)	Key Change Reasons/ Justification for Change
	Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020 Feb;43(2):487-93.		
Appendix C	*New Appendix.* *Added appendix to consolidate the signs and symptoms of intercurrent illness and/or potential adverse events for subject/Investigator education and assessments into one location for ease of use.*		
SOC	*Removal of all previous SOCs* *Moving forward only the most recent SOC will be included in the protocol.*		

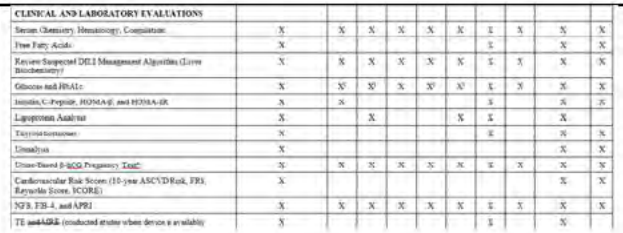
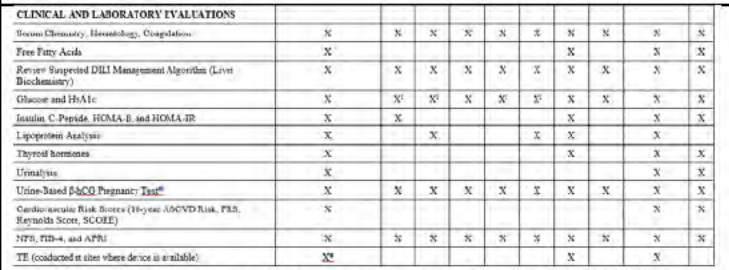
APPENDIX H. SUMMARY OF CHANGES: PROTOCOL VERSION 5.0 TO PROTOCOL VERSION 6.0 (DATED: 06 MAR 2020)

Protocol 747-304 was revised to include the following information:

1) DMC recommendation for treatment-emergent acute or nonacute pancreatitis
2) Highly effective contraception language per CTFG guidance
3) SUSAR definition per ICH guidance

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

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
Study Personnel Contact Information	Secondary Contact: [redacted] ~~MD~~ [redacted] Intercept Pharmaceuticals, Inc. Email: [redacted]	Secondary Contact: [redacted] **PharmD, MS** [redacted] **PV Monitoring** Intercept Pharmaceuticals, Inc. Email: [redacted]	Medical monitor secondary contact was updated to reflect change in personnel.
5.5 Summary of Known Potential Risks with Investigational Product	Following a request from the FDA ~~to provide an up-to-date DMC report analyzing unblinded data on respective incidence of cholecystitis, cholelithiasis, and pancreatitis by treatment group across all ongoing clinical studies~~, an ad hoc DMC review was held and the DMC recommended that: • ~~As it concerned pancreatitis, all studies continue without changes~~. • For subjects in Study 747-303, investigational product should be ~~uninterrupted~~ in subjects who experience symptomatic cholelithiasis and/or cholecystitis. The Sponsor decided to implement the DMC recommendations across the NASH program. Refer to the IB for additional information regarding the known potential risks with the investigational product.	Following a request from the FDA, an ad-hoc DMC review was held and the DMC recommended that: • For subjects in Study 747-303, investigational product should be **interrupted** in subjects who experience symptomatic cholelithiasis and/or cholecystitis. The Sponsor decided to implement the DMC recommendation across the NASH program. Refer to the IB for additional information regarding the known potential risks with the investigational product.	Moved to Section 7.5.2 which describes management of pancreatitis Corrected the typographical error of "uninterrupted".
Table 1 Schedule of Study Procedures (Double-Blind Phase)	Table 1: Schedule of Study Procedures (Double-Blind Phase) (Continued) 	Table 1: Schedule of Study Procedures (Double-Blind Phase) (Continued) 	Consistent with Section 9.9.10, a footnote was added to clarify

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
		[y] **If the subject completed a liver biopsy as part of the EOT visit, and remains in the study, a biopsy is not required at the Month 18 visit.**	that a liver biopsy is note required at Month 18 if the subject previously completed the EOT visit.
Table 2 Schedule of Study Procedures (OLE Phase)		 [n] **MRE will be conducted as part of the Month 18 DB EOT Visit**	MRE was removed and footnote was added per Protocol Version 5 Administrative Letter 1.
7.5 Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis or Pancreatitis	7.5. Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis NASH is associated with several known risk factors for cholelithiasis, such as obesity, type 2 diabetes, and other metabolic abnormalities. The prevalence of gallstone disease in NASH is higher than in the general population. The majority of gallstones are asymptomatic and may never become symptomatic. Because symptomatic events of cholelithiasis and/or cholecystitis may develop in subjects with or without a known history of gallstones, it is important that all subjects	7.5. Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis **or Pancreatitis** **7.5.1. Symptomatic Cholelithiasis and/or Cholecystitis** NASH is associated with several known risk factors for cholelithiasis, such as obesity, type 2 diabetes, and other metabolic abnormalities. The prevalence of gallstone disease in NASH is higher than in the general population. The majority of gallstones are asymptomatic and may never become symptomatic. Because symptomatic events of cholelithiasis and/or cholecystitis may develop in subjects with or without a known history of gallstones, it is important that all subjects be (1) monitored for	Based on a DMC review, information was added regarding pancreatitis as a condition associated with

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
	be (1) monitored for signs and symptoms suggestive of gallstone disease and (2) counseled to recognize and seek immediate medical attention if they experience symptoms suggestive of cholelithiasis and/or cholecystitis. If a subject experiences symptoms suggestive of cholelithiasis and/or cholecystitis, s/he should undergo a complete evaluation consistent with the local standard of care, be assessed for appropriate treatment, including potential indication for surgery (eg, cholecystectomy), and be monitored until resolution of clinical signs and symptoms. If symptomatic cholelithiasis and/or cholecystitis is diagnosed, investigational product should be interrupted (see Section 7.6).	signs and symptoms suggestive of gallstone disease and (2) counseled to recognize and seek immediate medical attention if they experience symptoms suggestive of cholelithiasis and/or cholecystitis. If a subject experiences symptoms suggestive of cholelithiasis and/or cholecystitis, s/he should undergo a complete evaluation consistent with the local standard of care, be assessed for appropriate treatment, including potential indication for surgery (eg, cholecystectomy), and be monitored until resolution of clinical signs and symptoms. If symptomatic cholelithiasis and/or cholecystitis is diagnosed, investigational product should be interrupted (see Section 7.6). **7.5.2. Pancreatitis** **Pancreatitis is a serious and potentially fatal condition most commonly caused by gallstones or alcohol.** **Because symptoms of acute pancreatitis and acute cholecystitis may be similar, subjects presenting with significant upper abdominal pain with nausea, vomiting, or fever should be evaluated for both cholecystitis and pancreatitis, consistent with the local standard of care (eg, amylase and lipase laboratory tests and/or imaging assessments).** **Investigational product must be permanently discontinued in any subject diagnosed with treatment-emergent acute, or nonacute (chronic or recurrent) pancreatitis. The evidence used to diagnose pancreatitis, including symptoms, laboratory test results, and/or imaging results, should be collected. 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 of treatment-emergent acute or nonacute pancreatitis.**	gallstone disease. Additionally, instructions were added to discontinue IP for treatment-emergent pancreatitis.

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		Investigational product discontinuation is not required for subjects who have a medical history of pancreatitis and have not experienced recurrence of pancreatitis since enrollment into the study. Any subject who meets the requirements for investigational product discontinuation should be encouraged to remain in the study and complete all protocol-specific assessments as defined, after stopping investigational product.	
7.6 Investigational Product Dosage Interruption, Downtitration, Discontinuation, and Rechallenge Criteria	Investigational product should not be interrupted in the following instances: 1) in subjects who previously experienced an event of symptomatic cholelithiasis and/or cholecystitis, and in whom symptoms have fully resolved at the present time while on ~~IP~~; 2) in subjects who experience an event that is not symptomatic (such as an incidental finding of gallstones during an ultrasound exam); ~~or~~ 3) in subjects who have already undergone a cholecystectomy following a prior event of cholelithiasis or cholecystitis (and who have no symptoms suggestive of retained or recurrent bile duct stones)..	Investigational product should not be interrupted in the following instances: 1) in subjects who previously experienced an event of symptomatic cholelithiasis and/or cholecystitis, and in whom symptoms have fully resolved at the present time while on **investigational product**; 2) in subjects who experience an event that is not symptomatic (such as an incidental finding of gallstones during an ultrasound exam); 3) in subjects who have already undergone a cholecystectomy following a prior event of cholelithiasis or cholecystitis (and who have no symptoms suggestive of retained or recurrent bile duct stones); **or 4) in subjects who have a medical history of pancreatitis and have not experienced a recurrence of pancreatitis since enrollment into the study.**	Based on the DMC recommendation for study 747-303, and the Sponsor's decision to extend this to the NASH program, IP will be discontinued in subjects who have treatment-emergent pancreatitis, and not in subjects who have a medical history of

<table>
<tr><th>Section</th><th>Original Text (Version 5.0, 19 Jul 2019)</th><th>Revised Text (Version 6.0, 06 Mar 2020)</th><th>Key Change Reasons/ Justification for Change</th></tr>
<tr><td></td><td></td><td></td><td>pancreatitis and did not experience treatment emergent pancreatitis while taking IP.</td></tr>
<tr><td>7.6, Table 5 Criteria for Dose Interruption, Discontinuation Downtitration and Rechallenge</td><td>
<table>
<tr><th colspan="3">DOSE DISCONTINUATION</th></tr>
<tr><th>Criteria</th><th>Action Taken with IP</th><th>Rechallenge</th></tr>
<tr><td>Potential Hepatic Decompensation[e] or Progression to Child Pugh B or C [CP Score ≥7]</td><td>Discontinue[f] / No Rechallenge</td><td>Continue to return for scheduled study visits for safety follow up; however, the subject should not be rechallenged. Monitor closely for clinical outcomes according to protocol assessments.</td></tr>
<tr><td>≥Grade 3 pruritus[g]</td><td rowspan="4">Discontinue[f] / No Rechallenge</td><td rowspan="4">Continue to return for scheduled study visits for safety follow up; however, the subject should not be rechallenged.</td></tr>
<tr><td>Other AEs ≥Grade 3 considered possibly, probably, or definitely related to IP</td></tr>
<tr><td>Liver transplantation</td></tr>
<tr><td>Bariatric Surgery</td></tr>
</table>
</td><td>
<table>
<tr><th colspan="3">DOSE DISCONTINUATION</th></tr>
<tr><th>Criteria</th><th>Action Taken with IP</th><th>Rechallenge</th></tr>
<tr><td>Potential Hepatic Decompensation[e] or Progression to Child Pugh B or C [CP Score ≥7]</td><td>Discontinue[f] / No Rechallenge</td><td>Continue to return for scheduled study visits for safety follow up; however, the subject should not be rechallenged. Monitor closely for clinical outcomes according to protocol assessments.</td></tr>
<tr><td>Treatment-emergent acute or nonacute pancreatitis</td><td rowspan="4">Discontinue[f] / No Rechallenge</td><td rowspan="4">Continue to return for scheduled study visits for safety follow up; however, the subject should not be rechallenged.</td></tr>
<tr><td>≥Grade 3 pruritus[g]</td></tr>
<tr><td>Other AEs ≥Grade 3 considered possibly, probably, or definitely related to IP</td></tr>
<tr><td>Liver transplantation</td></tr>
</table>
</td><td>Added IP discontinuation in subjects who have treatment-emergent pancreatitis to table with other criteria for IP discontinuation.</td></tr>
</table>

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
		Bariatric Surgery	
8.1.1 Study Inclusion Criteria	3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Female subjects are considered as being of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Effective methods of contraception are listed below: • Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm with spermicide; or • Intrauterine device; or • Vasectomy (partner); or • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or • Abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse)	3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Female subjects are considered as being of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Effective methods of contraception are listed below **(refer to Section 9.8 for highly effective contraceptive methods)**: • Barrier method, ie, (a) condom (male or female) with spermicide or (b) diaphragm with spermicide; or • Intrauterine device; or • Vasectomy (partner); or • Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection); or • Abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse)	Added in reference to new language on highly effective contraceptive methods.
8.2 Withdrawal Criteria	Refer to Section 7.4 for withdrawal criteria related to potential hepatic injury and/or decompensation; progression to cirrhosis with CP score ≥7; Grade 3 pruritus, AEs ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product; AEs ≥Grade 4 in severity	Refer to Section 7.4 **and Section 7.5** for withdrawal criteria related to potential hepatic injury and/or decompensation; progression to cirrhosis with CP score ≥7; **treatment-emergent acute or nonacute pancreatitis;** Grade 3 pruritus, AEs ≥Grade 3 in severity and possibly, probably, or definitely related to	Language regarding pancreatitis added for

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	and NOT or unlikely related to investigational product; liver transplantation, bariatric surgery, and pregnancy. Other reasons, including withdrawal of consent or lost to follow up and withdrawal from [redacted], are described in Section 8.2.1 below.	investigational product; AEs ≥Grade 4 in severity and NOT or unlikely related to investigational product; liver transplantation, bariatric surgery, and pregnancy. Other reasons, including withdrawal of consent or lost to follow up and withdrawal from [redacted], are described in Section 8.2.1 below.	consistency with Table 5.
9.8 Highly Effective Contraception	9.7. Restrictions No additional restrictions. ~~9.8~~. Visit Procedures	9.7. Restrictions No additional restrictions. **9.8. Highly Effective Contraception** **Recent guidelines recommend "highly effective" contraception measures for investigational products with limited or no human data available on pregnancies. (HMA CTFG 2014). Highly effective methods of contraception per the CTFG guidelines are those that alone or in combination result in a failure rate of less than 1% per year when used consistently and correctly. The highly effective contraception measures should be maintained during treatment and until the end of relevant systemic exposure. Women of child-bearing potential, currently enrolled in the 747-304 study, will employ the highly effective contraception measures during treatment with IP for their participation in the study.** **Female subjects must be postmenopausal, surgically sterile, or, if premenopausal (and not surgically sterile), be prepared to use at least one highly effective method of contraception during the study and for 30 days after the end of treatment. Highly effective methods of contraception include the following:** • **Intrauterine device (IUD)** • **Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • **Vasectomy (male partner)** • **Combined (estrogen- and progestogen-containing) hormonal contraception (eg, oral, intravaginal or transdermal) associated with inhibition of ovulation.**	Based on recent guidelines, instructions for highly effective contraception were added to supplement the information on contraception described in the inclusion criteria for female subjects of childbearing potential who are already

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
		• **Progestogen-only hormonal contraception (eg, oral, injectable or implantable) associated with inhibition of ovulation.** • **Sexual abstinence, if in line with the preferred and usual lifestyle of the subject (where abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments).** **9.9.** Visit Procedures	enrolled in the study.
9.9.10 DB Month 18/EOT/EOS/OLE Day 1 Visit for Subjects Continuing into the OLE	• Liver biopsy (must be completed prior to dosing with investigational product at Day 1 OLE).	• Liver biopsy (must be completed prior to dosing with investigational product at Day 1 OLE). **If the subject completed a liver biopsy as part of the EOT visit, and remains in the study, a biopsy is not required at the Month 18 visit**.	Added clarification regarding a liver biopsy at Month 18 if the subject has completed the EOT visit.
9.9.13 OLE Month 6	• Noninvasive radiological liver fibrosis measurements (TE ~~and MRE~~; conducted at sites where device is available; ~~MRE only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects)~~	• Noninvasive radiological liver fibrosis measurements (TE; conducted at sites where device is available)	MRE was removed and footnote was added per Protocol Version 5 Administrative Letter 1.

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
9.9.14 OLE Month 12/EOT/EOS	• Noninvasive radiological liver fibrosis measurements (TE ~~and MRE~~; conducted at sites where device is available; ~~MRE only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects)~~	• Noninvasive radiological liver fibrosis measurements (TE; conducted at sites where device is available)	MRE was removed and footnote was added per Protocol Version 5 Administrative Letter 1.
15.1.2 Suspected Unexpected Serious Adverse Reaction	15.1.1.3. Serious Adverse Event An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: • Death • Is immediately life threatening • Requires in-subject hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability or incapacity • Results in a congenital abnormality or birth defect • Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above Events not considered to be SAEs are hospitalizations for: • Routine monitoring of the studied indication and not associated with any deterioration in condition or AE • Elective treatment for a pre-existing condition that did not worsen • Respite care or observation when there is no AE associated with the hospitalization ~~15.1.2.~~ Relationship to Investigational Product	15.1.1.3. Serious Adverse Event An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: • Death • Is immediately life threatening • Requires in-subject hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability or incapacity • Results in a congenital abnormality or birth defect • Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above Events not considered to be SAEs are hospitalizations for: • Routine monitoring of the studied indication and not associated with any deterioration in condition or AE • Elective treatment for a pre-existing condition that did not worsen • Respite care or observation when there is no AE associated with the hospitalization **15.1.2. Suspected Unexpected Serious Adverse Reaction**	The definition of SUSAR was added to the protocol according to the ICH GCP guidelines that state the Sponsor should expedite the reporting to all concerned including the Investigator(s)/instit

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
		A SUSAR is defined as a suspected adverse reaction which is assessed as serious, causally related to the investigational medicinal product, and unexpected per the reference safety information (RSI) in the Investigator's Brochure. **SUSARs are subject to expedited reporting. The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening are 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. 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 15 days of first knowledge by the sponsor. Each competent authority shall ensure that all SUSARs to an investigational medicinal product which are brought to its attention are recorded. The sponsor shall also inform all participating investigators, as applicable to the local regulations.** **15.1.3.** Relationship to Investigational Product	utions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all ADRs that are both serious and unexpected.
15.1.8 Suspected Liver-Related Clinical Outcome Events	Specified liver-related clinical outcome events may, by definition (see Section 15.1.1.3) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section ~~15.1.6.2~~). The Sponsor is responsible for regulatory reporting of SAEs, including expeditious reporting of SUSARs, ~~which are defined as SAEs that are considered related (definitely, probably, or possibly related) to the investigational product and considered unexpected as defined in the IB.~~	Specified liver-related clinical outcome events may, by definition (see Section 15.1.1.3) qualify as SAEs. The Sponsor must be notified of any SAEs within 24 hours of the site becoming aware of the event (see Section **15.1.7.2**). The Sponsor is responsible for regulatory reporting of SAEs, including expeditious reporting of SUSARs, **refer to Section 15.1.2 for the definition of SUSAR.**	Definition of SUSAR updated for consistency with ICH guidance defined in Section 15.1.2.

Section	Original Text (Version 5.0, 19 Jul 2019)	Revised Text (Version 6.0, 06 Mar 2020)	Key Change Reasons/ Justification for Change
15.1.12 Follow-Up of AEs and SAEs	15.1.12. Follow-Up of AEs and SAEs 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. ~~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.~~	14.1.11. Follow-Up of AEs and SAEs **If a subject experiences symptoms consistent with cholelithiasis or pancreatitis, the subject should undergo a complete evaluation for both conditions consistent with local standards of care. If symptomatic cholelithiasis and/or cholecystitis is diagnosed, investigational product should be interrupted, and the subject should be managed and monitored as described in Section 7.5.1.** 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. **If treatment-emergent acute or nonacute pancreatitis is diagnosed, investigational product must be discontinued, and the subject should be managed and monitored as described in Section 7.5.2.** The Investigator should contact the Medical Monitor upon awareness **of pancreatitis**. Results should be recorded promptly in the eCRF.	This provides further instructions for the Investigator for IP discontinuation and follow-up in subjects diagnosed with treatment-emergent pancreatitis.
22 References	Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., Badia, X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res. 20(10), 1727–1736 (2011) Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995 Jun;22(6):696-9.	Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., Bonsel, G., Badia, X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res. 20(10), 1727–1736 (2011) **Human Medicines Agency, Clinical Trial Facilitation Group (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Retrieved from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf accessed 27 Jan 2020.** Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995 Jun;22(6):696-9.	Added reference for the most recent guidance for highly effective contraception in subjects participating in clinical trials.

APPENDIX G. SUMMARY OF CHANGES: PROTOCOL VERSION 4.0 TO PROTOCOL VERSION 5.0 (DATED: 19 JULY 2019)

Protocol 747-304 was revised to include the following information:

1. The Double-Blind Phase was extended from 12 months to 18 months, with the addition of study visits at Month 15 and Month 18.
2. Total enrollment was expanded from 540 subjects to 900 subjects

[redacted]

4. Additional criteria for uptitration at Month 3 were included

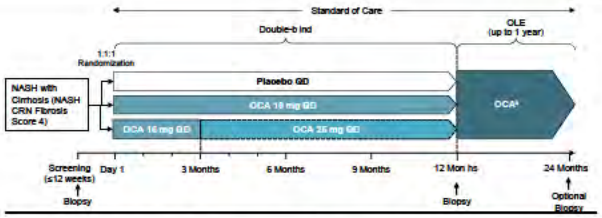
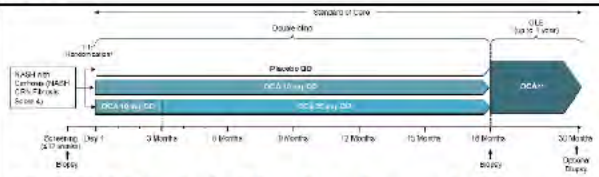
The text deleted from Protocol Version 4.0 is crossed out and revised text in Version 5.0 is indicated in bold font in the following table. Each revision also includes a reason or justification for the change. Section numbers refer to Version 5.0 unless otherwise stated. Sections with extensive changes that are discussed elsewhere have been summarized rather than highlighting exact changes. Minor changes including typos or editorial revisions are not listed individually in the following table.

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
Study Personnel Contact Information	[redacted] MD [redacted] Intercept Pharmaceuticals, Inc. [redacted]	[redacted] MD [redacted] Intercept Pharmaceuticals, Inc. [redacted]	Change in study personnel contact information.
Synopsis: Studied Period/Duration of Treatment/Criteria for Evaluation/Efficacy Analysis *and* Section 6 Study Objectives and Purpose *and* Section 7.1.3 Study Duration *and* Section 11 Overview of Assessments *and* Section 16.3 Primary Efficacy Analysis	The maximum duration of individual subject participation for this study is approximately 2 years and ~~3~~ months, including a Screening Period of up to 12 weeks, ~~a 1 year~~ Double-Blind Phase, and an ~~optional~~ Open-Label Extension (OLE) expected to last approximately 1 year.	The maximum duration of individual subject participation for this study is approximately 2 years and **6** months, including a Screening Period of up to 12 weeks, **an 18-month** Double-Blind Phase, and an Open-Label Extension (OLE) expected to last approximately 1 year.	EOS/EOT extended from Month 12 to Month 18 While a treatment duration of 12 months had initially been selected, emerging evidence suggests that 12 months may not be optimal to evaluate histological reversal of NASH cirrhosis. As such, the 18-month duration of the treatment period for Study 747-304 has been selected. "optional" removed as a redundancy

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
Synopsis: Objectives/Criteria for evaluation/Efficacy Analysis *and* Section 6.1: Primary Objectives *and* Section 11: Overview of Assessments *and* Section 16.3: Primary Efficacy Analysis	Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of Nonalcoholic Steatohepatitis (NASH) defined as no increase in hepatocellular ballooning or lobular inflammation, using the NASH Clinical Research Network (CRN) scoring system, from Baseline to Month ~~12~~	Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage with no worsening of Nonalcoholic Steatohepatitis (NASH) defined as no increase in hepatocellular ballooning or lobular inflammation, using the NASH Clinical Research Network (CRN) scoring system, from Baseline to Month **18**	EOS/EOT extended from Month 12 to Month 18
Synopsis: Objectives *and* Section 6.2 Secondary Objectives *and* Section 11 Overview of Assessments *and*	*Addition of a secondary objective*	• **NASH resolution based on overall pathologist interpretation (resolution of definite NASH) from Baseline to Month 18**	Emerging evidence suggests that overall pathologist interpretation is a more consistent and reproducible way to evaluate NASH

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
Section 16.5.1 Other Histology Endpoints			
Synopsis: Objectives/ Criteria for evaluation *and* Section 6.2: Secondary Objectives *and* Section 11: Overview of Assessments *and* Section 16.5.2: Clinical Outcomes	• Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint): – Death (all causes) – Liver transplant – ~~Hepatocellular carcinoma (HCC) as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy~~ – Model for end-stage liver disease (MELD) score ≥15 – Worsening of Child-Pugh (CP) score (by at least 2 points) – Hospitalization (as defined by a stay of ≥24 hours) for: o Variceal bleed o Hepatic encephalopathy (as defined by a West Haven score of ≥2) o Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) – Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) • Occurrence of individual components of outcome events	• Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint): – Death (all causes) – Liver transplant – Model for end-stage liver disease (MELD) score ≥15 – Worsening of Child-Pugh (CP) score (by at least 2 points) – Hospitalization (as defined by a stay of ≥24 hours) for: o Variceal bleed o Hepatic encephalopathy (as defined by a West Haven score of ≥2) o Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) – Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) • Occurrence of individual components of outcome events • **Occurrence of hepatocellular carcinoma (HCC) as confirmed by 2 complementary imaging modalities unless already confirmed by biopsy**	HCC is not considered part of the composite endpoint so it was listed separately
Synopsis: Objectives/Crit	The effect of OCA treatment compared to placebo on the following additional measures and markers:	The effect of OCA treatment compared to placebo on the following additional measures and markers:	To differentiate from liver function

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
eria for Evaluation *and* Section 6.2 Secondary Objectives *and* Section 11 Overview of Assessments	• Liver biochemistry and function	• Liver biochemistry and **synthetic** function	[redacted]
Synopsis: Objectives *and* Section 6.2: Secondary Objectives	• The PK/pharmacodynamic (PD) relationships of OCA and its conjugates • Safety and tolerability	• The PK/pharmacodynamic (PD) relationships of OCA and its conjugates • **The effect of OCA treatment on liver function using [redacted] (conducted at US sites where capable)** • Safety and tolerability	[redacted] was added as a substudy at US sites where capable
Synopsis: Open-Label Extension *and* Section 7.1 Overall Study Design *and* Section 9.2.2 OLE Phase	Subjects who complete the Double-Blind Month ~~12~~ Visit (and continue to receive investigational product) are eligible to enroll into the OLE. All subjects will receive OCA upon entry into the OLE. Subjects randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). ~~Uptitration will be based on the safety and tolerability assessments completed prior to Month 3.~~ Subjects randomized to OCA (10 mg or 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase; however, they will undergo dummy titration to maintain study blind until all subjects complete the Double-Blind Phase and the database is locked.	Subjects who complete the Double-Blind Month **18** Visit and continue to receive investigational product are eligible to enroll into the OLE. All subjects will receive OCA upon entry into the OLE. Subjects randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). **Uptitration will be determined based on the same criteria and assessments as employed in the Double-Blind Phase.** Subjects randomized to OCA (10 mg or **10 mg** → 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase; however, they will undergo dummy titration to maintain study blind until all subjects	Edited for clarity

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
		complete the Double-Blind Phase and the database is locked.	
Synopsis Study Design Diagram *and* Section 7.1.1: Study Design Diagram	 CP = Child-Pugh; CRN = clinical research network; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = once daily. [a]All subjects will receive OCA upon entry into the OLE [b]During the OLE period, subjects will return for site visits at Months 1, 2, 3, 4, 5, 6, 9, and 12.	 CP = Child-Pugh; CRN = clinical research network; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = once daily. [a] **Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with the standard of care.** [b] All subjects will receive OCA upon entry into the OLE: **Subjects who received placebo during the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). Subjects who received OCA during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase.** [c] During the OLE period, subjects will return for site visits at Months 1, 2, 3, 4, 5, 6, 9, and 12.	EOS/EOT extended from Month 12 to Month 18, Month 15 and Month 18 visits added. Footnotes edited to specify randomization
Synopsis Study Design Diagram *and*	Notes: • Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH (determined by central reading of liver histology) will be enrolled in the study. Subjects with hepatic decompensation or CP Class B or CP Class C cirrhosis are excluded.	Notes: • Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH (determined by central reading of liver histology) will be enrolled in the study. Subjects with hepatic decompensation or CP Class B or CP Class C cirrhosis are excluded.	

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
Section 7.1.1 Study Design Diagram: Overall Study Design	• Two screening visit assessments will be performed. Screening Visit 1 will occur no more than 12 weeks prior to Day 1, and Screening Visit 2 will occur at least 4 weeks after Screening Visit 1. • ~~Subjects without a liver biopsy obtained ≤12 months prior to Day 1 must have a biopsy completed during the screening period.~~ • Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). • ~~Subjects who received placebo during the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). Subjects who received OCA during the Double-Blind Phase will continue the same dosing regimen they received at the end of the Double-Blind Phase.~~ • The study will remain blinded until all subjects complete the Double-Blind Phase and the database is locked. To maintain blinding, all investigational product (placebo and OCA) tablets and bottles will be identical.	• Two screening visit assessments will be performed. Screening Visit 1 will occur no more than 12 weeks prior to Day 1, and Screening Visit 2 will occur at least 4 weeks after Screening Visit 1. • Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). • The study will remain blinded until all subjects complete the Double-Blind Phase and the database is locked. To maintain blinding, all investigational product (placebo and OCA) tablets and bottles will be identical.	Removed bullet points are addressed other places in the protocol. Note added to footnote of Diagram
Synopsis: Number of Subjects (planned)/ Enrollment and Randomization *and* Section 7.2 Number of Subjects	Approximately ~~540~~ subjects will be enrolled in the study	Approximately **900** subjects will be enrolled in the study	Enrollment expanded to 900 subjects

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
Synopsis Exclusion Criteria *and* Section 8.1.2 Subject Exclusion Criteria *and* Section 9.3 Concomitant Medications *and* Section 9.8.3 Screening Procedures	Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization. For alanine aminotransferase (ALT), aspartate aminotransferase (AST), ~~and total bilirubin for which if Screening Visit 1 and Visit 2 values differ by ≥30% and either of the lab values is > upper limit of normal (ULN), then a third sample will be collected at an unscheduled visit as a confirmatory sample.~~ Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment:	Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization. For alanine aminotransferase (ALT), aspartate aminotransferase (AST), **or total bilirubin (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome), if the Screening Visit 2 value is ≥30% higher than the Screening Visit 1 value and > the upper limit of normal (ULN), then a third measurement must be obtained at an unscheduled visit.** Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment:	Edited to clarify when a third measurement is necessary
	1. Current or past history of ~~hepatic decompensation such as clinically significant ascites (requiring medical intervention)~~, variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes	1. Current or past history of **a clinically evident hepatic decompensation event, such as ascites,** variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes	Edited for clarity
	6. AST ≥5× ~~upper limit of normal (~~ULN~~)~~	6. AST ≥5× ULN **a. If a third serum AST measurement is required, and both Screening Visit 2 and unscheduled visit AST values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment**	Edited for clarity
	7. ALT ≥5× ULN	7. ALT ≥5× ULN **a. If a third serum ALT measurement is required, and both Screening Visit 2 and unscheduled visit ALT values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment**	Edited for clarity

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	8. Calculated creatinine clearance <60 mL/min using Cockcroft-Gault method ~~at Screening~~ 9. Platelet count ≤100 000/mm^3 ~~at Screening~~ 10. Total bilirubin >2 mg/dL ~~(subjects with an established diagnosis of Gilbert's syndrome and a normal hemoglobin and reticulocyte count may be enrolled despite a total bilirubin level >2 mg/dL if their conjugated (direct) bilirubin is <2× ULN)~~ 13. International normalized ratio (INR) ≥1.7 ~~(subjects with a known inherited blood disorder and INR ≥1.7 may be enrolled, and subjects on anticoagulant/anti-aggregant treatment and INR ≥1.7 may be enrolled by approval of Medical Monitor)~~ 18. Evidence of other known forms of chronic liver disease including: – Positive test result at Screening for hepatitis B surface antigen	8. Calculated creatinine clearance <60 mL/min using Cockcroft-Gault method 9. Platelet count ≤100 000/mm^3 10. Total bilirubin >2 mg/dL **(except for subjects with an established diagnosis of Gilbert's syndrome, if hemoglobin and reticulocyte count are within the normal range and conjugated bilirubin is <1.5× ULN)** **a. If a third serum total bilirubin measurement is required (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome), both Screening Visit 2 and unscheduled visit values are ≥30% higher than the Screening Visit 1 value, the subject is ineligible for enrollment.** 13. International normalized ratio (INR) ≥1.7 18. Evidence of other known forms of chronic liver disease including: – Positive test result at Screening for hepatitis B surface antigen – Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at	"at Screening" is redundant in this section Exceptions for subjects with Gilbert's syndrome added to clarify that bilirubin entry criteria should be based on conjugated bilirubin levels rather than total bilirubin levels Removed allowance for enrollment of subjects on anticoagulants with INR >/= 1.7 due to potential artificial inflation of MELD/CP scores

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	– Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or confirmed history of a positive HCV RNA test result(s) – Primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome – Alcoholic liver disease – Wilson disease, hemochromatosis, or iron overload – Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion) – Prior known drug-induced liver injury within 5 years before Day 1 – Known or suspected HCC	Screening) or confirmed history of a positive HCV RNA test result(s) **except for subjects with evidence of spontaneous HCV eradication (defined as positive HCV antibodies at Screening, no history of positive HCV RNA result, and documentation that no anti-HCV therapy has been received)** – Primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome – Alcoholic liver disease – Wilson disease, hemochromatosis, or iron overload – Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion) – Prior known **or suspected** drug-induced liver injury within 5 years before Day 1 – Known or suspected HCC	Exception added to allow enrollment of subjects with a history of spontaneous HCV eradication Edited for clarity
	19. History of liver transplant, current placement on a liver transplant list 20. Hemoglobin A1c ≥9.5% within ~~60~~ days before Day 1	19. History of liver transplant, **or** current placement on a liver transplant **waiting** list 20. Hemoglobin A1c **(HbA1c)** ≥9.5% within **90** days before Day 1	Changed to align with 747-303 protocol

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	21. Low-density lipoprotein (LDL) cholesterol ≥190 mg/dL and already on a stable dose of ~~statin and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for ≥30 days at Screening~~	21. Low-density lipoprotein (LDL) cholesterol ≥190 mg/dL and already on a stable dose of **LDL-lowering medication for ≥30 days**	Expanded to any LDL-lowering medication
	22. LDL cholesterol <50 mg/dL ~~(irrespective of statin use)~~	22. LDL cholesterol <50 mg/dL **in subjects not on LDL-lowering medication**	Expanded to any LDL-lowering medication
	28. Chronic use (≥12 months) of drugs historically associated with drug-induced NAFLD within the 5 years before Day 1 (eg, amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins).	28. Chronic use (≥12 months) of drugs historically associated with drug-induced NAFLD within the 5 years before Day 1 (eg, amiodarone, methotrexate, systemic glucocorticoids **[unless used at physiologic replacement doses for the treatment of adrenal insufficiency],** tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids **[except for testosterone preparations used at physiologic replacement doses for the treatment of documented/confirmed hypogonadism]**, valproic acid, and other known hepatotoxins).	Exception added for adrenal insufficiency Exception added for hypogonadism
	Addition of criteria 37 and 38	**37. Alkaline phosphatase ≥1.5x ULN**	Added ALP exclusion based on FDA draft guidance for NASH cirrhosis (June 2019)
		38. History of known or suspected hypersensitivity to any ingredient in human albumin preparations (at US sites where [redacted] will be conducted)	[redacted]
Synopsis	*Clarification added*	**Specific details of the events that will be adjudicated by the Cardiovascular Adjudication Committee and**	Added for clarity

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
Event Adjudication *and* Section 16.11.2 Adjudicated Cardiovascular Events *and* Section 16.14 Adjudication Committees		**Hepatic Outcomes Committee 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.**	
Synopsis Criteria for Evaluation *and* Section 11: Overview of Assessments *and* Table 13 *And* Section 16 Statistics	Markers of cardiovascular safety Lipoproteins (LDL, HDL, VLDL, ApoB, ApoA-1, ApoE, Lp[a]), total cholesterol, triglycerides, PCSK9, cardiovascular risk scores (FRS, Reynolds score, and SCORE) Noninvasive assessments of liver disease assessed by serum markers and imaging tests: [redacted]: NFS, FIB-4, and APRI Noninvasive panel of circulating fibrosis markers: ELF~~,~~ ~~FibroMax~~, and FibroMeter Noninvasive radiological liver fibrosis measurements (conducted at sites where device is available): TE Fibroscan®, MRE PK/PD of OCA and conjugates	Markers of cardiovascular safety Lipoproteins (LDL, HDL, VLDL, ApoB, ApoA-1, ApoE, Lp[a]), total cholesterol, triglycerides, PCSK9, cardiovascular risk scores (**10-year ASCVD Risk,** FRS, Reynolds score, and SCORE) Noninvasive assessments of liver disease assessed by serum markers and imaging tests: Noninvasive scores of liver fibrosis: NFS, FIB-4, and APRI Noninvasive panel of circulating fibrosis markers: ELF, and FibroMeter Noninvasive radiological liver fibrosis measurements (conducted at sites where device is available): TE Fibroscan® and/or MRE **(only in subjects enrolled prior to Version 5 of the protocol who already had baseline MRE; not in newly enrolled subjects)** PK/PD of OCA and conjugates	10-year ASCVD Risk was added to the markers of cardiovascular safety Fibromax marker removed MRE will only be continued for subjects with a baseline measurement Edited for clarity

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	~~The exposure-response relationships between OCA PK and PD biomarkers of FXR activation and NASH~~ *Addition of HepQuant procedure*	**Exposure-response relationships between OCA PK and efficacy endpoint(s) along with PD markers of FXR activation** **Liver function assessment using HepQuant-SHUNT** **DSI, a marker of liver function, as assessed by HepQuant-SHUNT measures (conducted at US sites where capable)**	HepQuant Shunt was added as a substudy at US sites where capable
Synopsis Efficacy Analysis *And* Section 16.4 Secondary Efficacy Analysis	The type 1 error for the primary efficacy analysis will be controlled at ~~0.01~~.	The type 1 error for the primary efficacy analysis will be controlled at **0.05.**	As the study is testing a single hypothesis, a 2-sided type I error at 0.05 level is assumed with no multiplicity adjustment. Given Study 747-304 is designed to support a single study approval, the Sponsor acknowledges that the p value for the primary endpoint will need to be robust. Of note, this sample size will provide at least 80% probability to achieve a p-value < 0.01.

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Synopsis Pharmacodynamic Analyses *and* Section 16.5.8 HepQuant-Shunt	*Addition of HepQuant-SHUNT analysis*	[redacted]	HepQuant Shunt was added as a substudy at US sites where capable
Synopsis: Pharmacokinetic/Pharmacodynamic Analyses	~~A sequential approach will be used to perform the population PK/PD analysis. The Bayesian estimates of individual PK parameters from the final population PK model will be used to generate PK profiles for each subject. The change in each PD assessment (eg, C4, FGF-19) over time will be incorporated into a maximum effect (E_{max}) model with OCA dose level as an independent variable. Estimated model parameters for each individual will be derived from prior E_{max}, and the half maximal effective concentration values, and baseline measures of each PD assessment. The appropriate structure of the variance-covariance matrix will also be evaluated. Fixed and random effect parameter estimates and associated asymptotic standard errors will be estimated. Descriptive statistics will be used to summarize Bayesian estimates of PK/PD parameters obtained from individual assessments in the population PK/PD model. These PK/PD analyses will be reported in a separate document outside of the clinical study report.~~	**Exploratory plots for efficacy endpoints and markers of FXR activation versus plasma exposure of total OCA will be generated. A locally estimated scatterplot smoothing (LOESS) line will be used to assess potential relationships. Additional analyses, including maximum effect (E_{max}) models, may also be performed based on the exploratory results. Details of these analyses will be specified in the statistical analysis plan and/or clinical pharmacology analysis plan.**	PK/PD analysis updated
Synopsis Sample Size Justification *and* Section 16.2:	~~A sample size of 180 subjects per group with an assumed 5% discontinuation rate will provide 90% power to demonstrate a statistically significant treatment difference between OCA 25 mg and placebo groups based on Chi-square test with 2-sided type I error at 0.01 level. This assumes a responder rate of 23% and 8% in the OCA and~~	**A sample size of 300 subjects per group will provide at least 90% power to detect a statistically significant treatment difference of 10% between OCA 25 mg and placebo groups based on a Chi-square test with 2-sided type I error at 0.05 level, assuming a responder rate of 10% in the placebo group. As**	Enrollment expanded to 900 subjects and adjustment of type 1 error

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Determination of Sample Size	~~placebo groups, respectively, based on data from literature, observed effect size on fibrosis improvement in advanced fibrosis subjects in the Farnesoid X receptor Ligand OCA in Nonalcoholic Steatohepatitis Treatment (FLINT) study and practical consideration.~~	**there was no previous study performed using the same endpoint in this disease, the assumption was determined based on data from literature, and results from the Farnesoid X receptor Ligand OCA in Nonalcoholic Steatohepatitis Treatment (FLINT) study and Study 747-303.**	
Section 5.1 Overview of Nonalcoholic Steatohepatitis and Obeticholic Acid	~~Despite the seriousness of the disease, there are currently no approved therapies for the treatment of NASH nor an accepted standard of care. The therapeutic options for NASH are largely limited to lifestyle modifications and treatment of concurrent conditions such as diabetes (Neuschwander-Tetri 2003, Belfort 2006, Sanyal 2010, Chalasani 2012). For patients with NASH without diabetes, practice guidelines from the American Association for the Study of Liver Diseases recommend the use of vitamin E as first line therapy (Chalasani 2012).~~ ~~However~~, there are currently no approved treatments ~~targeting the underlying pathophysiology, of progressive fibrosis or cirrhosis~~. Obeticholic acid (OCA) is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary bile acid chenodeoxycholic acid (CDCA). OCA's potent FXR agonist effects make it an attractive novel therapeutic agent for NASH due to its multiple FXR-mediated effects including ~~an increase in insulin sensitivity, glucose and lipid metabolism, hepatocyte protection against bile acid-induced cytotoxicity, anti-inflammatory effects in~~	**Despite the seriousness of the disease**,**especially when advance fibrosis/cirrhosis is present,** there are currently no approved **pharmacologic** treatments. Obeticholic acid (OCA) is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary bile acid chenodeoxycholic acid (CDCA**), the natural human FXR ligand.** OCA's potent FXR agonist effects make it an attractive novel therapeutic agent for NASH due to its multiple FXR-mediated effects, including prevention and reversal of liver fibrosis**, anti-inflammatory effects in liver and vasculature, and hepatocyte protection against bile-acid-induced cytotoxicity. Specifically,**	Edited for succinctness

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	~~liver and vasculature, and~~ prevention and reversal of liver fibrosis (Adorini 2012, Mudaliar 2013). ~~Specifically, nonclinical studies have shown several potentially beneficial properties of FXR agonism in NASH.~~	**nonclinical studies have shown several potentially beneficial properties of FXR agonism in NASH and cirrhosis** (Adorini 2012, Mudaliar 2013).	
Section 5.2 Nonclinical Experience with OCA	~~In addition, OCA plays a broad role in improving glycemic, metabolic, and cardiovascular parameters:~~ ~~• FXR plays a role in bile acid homeostasis, metabolism, and clearance (Cariou 2006, Ma 2006, Zhang 2008).~~ ~~• FXR controls glucose metabolism through regulation of gluconeogenesis and glycogenolysis in the liver, as well as regulation of peripheral insulin sensitivity in striated muscle and adipose tissue (Zhang 2006).~~ ~~• In nonclinical models, FXR agonism is associated with beneficial effects on body weight and composition (Fu 2004, Xu 2009).~~ ~~• The absence of endogenous intact FXR signaling results in dyslipidemia and a hepatic phenotype similar to NASH patients (Zhang 2008). Conversely, FXR agonists lower plasma triglycerides by repressing hepatic sterol regulatory element binding protein 1-c (Watanabe 2004) and increased hepatic fatty acid oxidation (Savkur 2005).~~	In summary, there is strong rationale to advance OCA for the treatment of NASH based on its FXR-mediated hepatoprotective properties.	Edited for succinctness

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	~~• In addition, OCA and other FXR agonists are anti-atherogenic and cardioprotective in animal models (Miyazaki-Anzai 2010, Hartman 2009).~~ In summary, there is strong rationale to advance OCA for the treatment of NASH based on its FXR-mediated hepatoprotective properties~~, anti-fibrotic effects in a NASH model, and results indicating that OCA improves glycemia by increasing peripheral glucose uptake, enhancing glucose-stimulated insulin secretion, and inhibiting hepatic lipid synthesis and content while inducing lipid uptake by adipocytes~~.		
Section 5.3 Clinical Experience with Obeticholic Acid	~~OCA is under investigation for the treatment of multiple chronic liver diseases, including the treatment of NASH, primary biliary cholangitis (PBC, also called primary biliary cirrhosis) [Beuers 2015a, Beuers 2015b, Beuers 2015c]), primary sclerosing cholangitis, biliary atresia, and other chronic liver diseases. OCA was granted accelerated approval by the United States Food and Drug Administration (FDA) on 27 May 2016. Conditional approvals were obtained on 12 Dec 2016 in the European Union (EU), and by Health Canada on 24 May 2017 under the trademark Ocaliva for the treatment of PBC~~ in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.	**OCA (Ocaliva) has received marketing authorization in the United States, Europe, Canada, and several other countries for the treatment of primary biliary cholangitis (PBC)** in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. **OCA is currently being developed for the treatment of multiple chronic non-viral liver diseases, including the treatment of NASH with fibrosis, NASH with cirrhosis, primary sclerosing cholangitis, and biliary atresia.**	Edited for clarity

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	The clinical development program for OCA in subjects with NAFLD or NASH includes data from the following 4 completed studies: • ~~Double Blind Phase of~~ Study 747-209: A Phase 2, double-blind, randomized, placebo-controlled, multicenter study evaluating the effect of OCA, and the subsequent addition of statin therapy, on lipoprotein metabolism in subjects with NASH with fibrosis stage 1 to 4, but no evidence of hepatic decompensation. *Addition of studies 747-117 and 747-118* Low-density lipoprotein (LDL) cholesterol demonstrated a modest but significant increase in subjects treated with	The clinical development program for OCA in subjects with NAFLD or NASH includes data from the following **6** completed studies: • Study 747-209: A Phase 2, double-blind, randomized, placebo-controlled, multicenter study evaluating the effect of OCA, and the subsequent addition of statin therapy, on lipoprotein metabolism in subjects with NASH with fibrosis stage 1 to 4, but no evidence of hepatic decompensation. • **Study 747-117: A Phase 1, double-blind, randomized, placebo-controlled study evaluating the safety, pharmacokinetics, and pharmacodynamics of OCA in subjects with NASH fibrosis.** • **Study 747-118: A Phase 1, single-center, double-blind, randomized study evaluating the safety, pharmacokinetics, and pharmacodynamics of OCA in healthy subjects and subjects with compensated Child-Pugh (CP) Class A cirrhosis due to NASH.** – **Including a 747-118 hepatic PK substudy in subjects with cirrhosis due to NASH.** Low-density lipoprotein (LDL) cholesterol demonstrated a modest but significant increase in	Study 209 has been completed 747-117 and 747-118 have been completed

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	OCA compared to placebo; however, this increase was reversed and LDL cholesterol returned to below baseline levels in subjects who initiated statin therapy. ~~The change in lipid profile, which was attenuated with continued treatment and reversed post-treatment, needs to be further investigated mechanistically and with respect to clinical management with standard of care statin therapy.~~ The general adverse event (AE) profile was similar ~~across both~~ groups, with the exception of pruritus.	subjects treated with OCA compared to placebo; however, this increase was reversed and LDL cholesterol returned to below baseline levels in subjects who initiated statin therapy. The general adverse event (AE) profile was similar **between the OCA 25 mg and placebo** groups, with the exception of pruritus.	Description of effects of OCA on lipid metabolism from study 747-209 edited for clarity
	~~Study 747-209 enrolled subjects with histological evidence of definite or probable NASH confirmed by liver biopsy and a nonalcoholic fatty liver disease activity score (NAS) of 4 or greater, randomized in a 1:1:1:1 ratio to receive OCA 5 mg, OCA 10 mg, OCA 25 mg or placebo, orally once daily, for 16 weeks. Randomization was stratified by LDL concentration (fasting serum low-density lipoprotein (LDL) cholesterol at Screening Visit 2; ≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4). Statin-free subjects as well as statin-treated subjects (following a 4-week statin washout) were eligible for enrollment. All subjects initiated treatment with atorvastatin at a dose of 10 mg once daily after 4 weeks of OCA treatment. After 4 weeks of 10 mg atorvastatin treatment, dosing was increased to 20 mg once daily, and continued for an additional 4 weeks. After 4 weeks of treatment at 20 mg daily dose, atorvastatin dosing could be titrated up or down as clinically indicated.~~	**Study 747-209 further evaluated the effect of OCA and atorvastatin treatment on LDL metabolism in subjects with NASH and liver fibrosis to better characterize the lipid profile changes observed in the FLINT study, as well as their management. Subjects with biopsy-confirmed NASH and fibrosis received placebo or OCA 5mg, 10 mg, or 25 mg once daily, for up to 4 weeks. Subjects initiated concurrent treatment with atorvastatin 10 mg once daily, titrated to 20 mg once daily at Week 8 based on tolerability. At Week 4, subjects experienced an approximately 20% to 25% increase in LDLc concentrations across all OCA groups. By Week 8, atorvastatin treatment effectively lowered LDLc to below baseline levels across all treatment groups. Together, these study results suggest that the risk of increases in LDLc with OCA use can generally be managed by statin use. Pruritus was the most**	Replaced with an updated summary of Study 747-209

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	~~A total of 84 subjects were randomized into the study, with baseline cirrhosis status being pre-cirrhotic in 62 (74%) subjects and cirrhotic in 22 (26%) subjects. Seventy-nine (94%) subjects completed the Double-Blind Phase. An increase in LDL cholesterol was observed following treatment with OCA and the addition of low-dose atorvastatin (10 mg) reversed OCA-associated changes in LDL cholesterol back to baseline levels and lower within 4 weeks.~~ ~~Three subjects discontinued due to AEs: 1 subject on OCA 5 mg for Stage 4 breast cancer, and 2 subjects on OCA 25 mg for pruritus.~~	**common AE and was dose dependent. Two subjects discontinued the study due to pruritus.** **Study 117 demonstrated that the PK profile of OCA in subjects with NASH fibrosis was consistent with what has been observed in healthy subjects and largely reflective of enterohepatic recirculation with exposure proportional to dose. Treatment with OCA 10 mg or 25 mg once daily for 12 weeks was found to be safe and well tolerated in NASH subjects with fibrosis (including fibrosis stage 1 through stage 4). The PD assessments demonstrated FXR activation and positive trends for select markers of fibrosis, inflammation, apoptosis, and liver function.** **Study 747-118 demonstrated that the safety profile of 10 mg and 25 mg doses of OCA in subjects with compensated CP Class A cirrhosis due to NASH was similar to the safety observed in healthy subjects, supporting their use in longer term efficacy studies. . The hepatic PK substudy demonstrated that OCA 25 mg was safe and generally well tolerated, showing improvements in the levels of liver biochemistry markers associated with hepatocellular injury when administered for 28 days to subjects with CP Class A cirrhosis due to NASH, consistent with results from the double blind period.**	Description of newly completed studies added

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	~~In addition, the~~ following studies evaluating OCA for the treatment of NASH are currently ongoing: • ~~The open label extension portion of Study 747-209.~~ • ~~A Phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter international study (Study 747-303) evaluating the safety and efficacy of OCA in precirrhotic subjects with NASH.~~	**The** following studies evaluating OCA for the treatment of NASH are currently ongoing: • **The clinical outcome portion of Study 747-303.** **A complete description of the OCA clinical development program is provided in the Investigator's Brochure.**	747-209 has been completed Update to 747-303 ongoing study
Section 5.4.1 Rationale for Study Design	NASH is a serious, chronic liver disease with a large unmet medical need and no approved therapies. ~~The incidence of NASH is increasing, and~~ NASH is likely to be the leading cause of liver transplant by 2020, highlighting the need for development of effective therapies that may improve steatohepatitis and fibrosis, potentially delaying liver transplant or death. ~~The FLINT study has demonstrated that OCA can improve individual features of steatohepatitis as well as fibrosis (Neuschwander-Tetri 2015).~~ As fibrosis has been consistently shown to be the strongest predictor of adverse clinical outcomes, including liver-related death, it is critical to prevent further progression of fibrosis and preferably reverse fibrosis. ~~The effects of OCA on fibrosis are currently being evaluated in a Phase 3 study in subjects with NASH and liver fibrosis. Patients with cirrhosis in the spectrum of NASH disease continuum represent the highest~~	NASH is a serious, chronic liver disease with a large unmet medical need and no approved therapies. **Patients with cirrhosis in the spectrum of NASH disease continuum represent the highest unmet medical need and are at the greatest risk of disease progression.** NASH is likely to be the leading cause of liver transplant by 2020, highlighting the need for development of effective therapies that may improve steatohepatitis and fibrosis, potentially delaying liver transplant or death. As fibrosis has been consistently shown to be the strongest predictor of adverse clinical outcomes, including liver-related death, it is critical to prevent further progression of fibrosis and preferably reverse fibrosis. **Results from FLINT and the 18-month interim analysis of Study 747-303 have demonstrated that OCA has robust anti-fibrotic**	Rationale expanded and clarified.

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	~~unmet medical need and are at greatest risk of disease progression. Thus,~~ Study 747-304 will evaluate efficacy and safety of OCA in subjects with ~~histological evidence of NASH with~~ cirrhosis (defined by a NASH Clinical Research Network [CRN] score of 4), ~~with the exception of subjects with hepatic decompensation or~~ Child-Pugh (CP) score ≥7. ~~The efficacy of OCA in this study will be evaluated based on histological improvement in fibrosis.~~	**effects and improves underlying disease activity and steatohepatitis in NASH subjects with fibrosis at the 18 month assessment. .** Study 747-304 will evaluate efficacy **(based on histological improvement in fibrosis)** and safety of OCA in **NASH** subjects with **compensated** cirrhosis (defined by a NASH Clinical Research Network [CRN] score of 4), **and** C (CP) score <7.	
Section 5.4.3 Rationale for Obeticholic Acid Doses and Duration	*Removal of a paragraph* ~~The duration of the 12-week titration is based upon results seen in the prior PBC program which effectively demonstrated titration for biologically altering the FXR signaling pathways thus inducing bile acid levels. Overall study duration was determined based on findings in prior NASH studies ranging from 6 months to 72 weeks. While the largest Phase 2 study of OCA in NASH patients was conducted over a period of 72 weeks, recent reports suggest that fibrosis improvement can be observed earlier than 72 weeks (Sanyal 2016, Loomba 2016). Modest decreases of serum markers of fibrosis (hyaluronic acid [HA], procollagen III amino terminal peptide [P3NP], and tissue inhibitor of metalloproteinase 1 [TIMP-1]) were seen after only 6 weeks of OCA 25 mg treatment (Study 747-203). Furthermore, in FLINT, OCA demonstrated reductions in fibrosis scores as early as 6 months after treatment with OCA, and these reductions were associated with histologic fibrosis improvement at 72 weeks. Therefore, it is~~		Rationale updated to reflect new information from the program

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	~~reasonable to expect that a 12-month placebo-controlled treatment period is sufficient to demonstrate an OCA treatment effect and a pattern of responses in this study population (Chalasani 2012).~~ *Addition of 18 Month treatment duration rationale*	**Rationale for Treatment Duration of 18 Months** **The natural history of NASH with liver fibrosis shows that both progression and regression of liver fibrosis are slow processes that may take years to develop as well as to improve. A systematic review and meta-analysis of paired-biopsy studies has shown that a 1-stage change in fibrosis occurs over a median of 7.1 years in patients with NASH (Singh 2015). Regression of fibrosis in established NASH cirrhosis is expected to take even longer (Cheung 2019). To date, no clinical trial in subjects with NASH cirrhosis has demonstrated efficacy with respect to reversal of cirrhosis and there are no approved treatment options for NASH cirrhosis.** **As presented above, OCA has shown robust anti-fibrotic effects based on histologic endpoints in pre-cirrhotic NASH subjects with liver fibrosis. A treatment duration of 12 months was initially selected for the placebo-controlled portion of this study based on non-histological data (using serum biomarkers of fibrosis observed in Study 747-203 and FLINT). However, the effects of OCA on liver histology at earlier time points, including 12 months, had not been assessed. The preliminary results of the 18-month interim analysis from Study 747-303 showed that OCA 25 mg was superior to placebo,**	

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		demonstrating histological improvement of NASH fibrosis without worsening of NASH with an effect size of ~11% over 18 months of treatment (Younossi 2019). However, the results also highlighted the slow process of regression of liver fibrosis and the potential challenges of demonstrating efficacy in regression of liver fibrosis within a finite time period. To reduce the chance of a false negative study, based on the above considerations, the duration of treatment in the double-blind phase has been extended to 18 months.	
Section 5.5.1 Risk/Benefit Profile of OCA in Subjects with NASH	An independent data monitoring committee (DMC) has performed detailed reviews of ~~several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification providing further support for the lack of safety concern and positive benefit-risk profile of OCA.~~	**An independent data monitoring committee (DMC) has performed detailed reviews of individual subject and aggregate data from both the Phase 3 clinical outcomes study in subjects with PBC (Study 747-302) and the Phase 3 pivotal studies in subjects with NASH fibrosis (Study 747-303) and NASH cirrhosis (Study 747-304) on a quarterly basis, in an unblinded fashion, and in closed sessions (without the Sponsor's participation). In the quarterly DMC meetings to date, the DMC has recommended the studies continue without modification.** **Following a request from the FDA to provide an up to date DMC report analyzing unblinded data on respective incidence of cholecystitis, cholelithiasis, and pancreatitis by treatment group across all**	Updated based on recent communication with the DMC

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		ongoing clinical studies, an ad hoc DMC review was held and the DMC recommended that: • **As it concerned pancreatitis, all studies continue without changes.** • **For subjects in Study 747-303, investigational product should be uninterrupted in subjects who experience symptomatic cholelithiasis and/or cholecystitis.** **The Sponsor decided to implement the DMC recommendations across the NASH program**	
Section 5.6 Importance of Monitoring of Disease Progression	~~NASH is a chronic, progressive liver disease; therefore, it is important that subjects with NASH are closely monitored to ensure early identification of potential disease progression to cirrhosis, decompensation and/or liver injury. The rate of progression and risk of decompensation is variable and may be rapid in certain patients necessitating closer surveillance of patients at risk. Therefore, more extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve subject oversight and safety. Investigators together with the Sponsor's Medical Monitor or designee will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or~~	**NASH is a chronic, progressive liver disease with variable rates of progression to cirrhosis and hepatic decompensation, although both may occur rapidly in certain patients. Subjects with NASH cirrhosis have accentuated risks relative to subjects with non-cirrhotic NASH and can transition abruptly from a clinically-compensated state to decompensated cirrhosis, with the manifestations of portal hypertension and impaired synthetic function that characterize end-stage liver disease. Subjects with NASH cirrhosis must therefore be closely monitored to ensure early identification of signs and symptoms of decompensation and/or liver injury. In this study, close and thorough safety monitoring is paired with appropriate investigational product dosing adjustment, interruption, and discontinuation to improve subject oversight and safety.**	Edited to provide rationale of uptitration criteria

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	~~decompensation coupled with rules-based laboratory monitoring.~~ ~~Subjects will be monitored for potential hepatic injury and/or progression to decompensation (Section 7.4). Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose adjustment are described in Section 7.6and Section 7.7. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.~~	**Investigators, together with the Sponsor's Medical Monitor or designee, will consistently and frequently assess individual subjects, including careful evaluation of signs, symptoms, and laboratory parameters to identify potential hepatic injury and/or decompensation. Criteria for potential hepatic injury and/or progression to decompensation are described in Section 7.4. Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures are described in Section 7.6 and Section 7.7.** **For subjects randomized to the uptitration arm, special consideration is given to monitoring and management of investigational product as discussed in more detail in Section 9.2. Uptitration criteria have been designed to ensure only subjects with evidence of adequate functional hepatic reserve will be exposed to the higher OCA dose (25 mg). Specifically, subjects may only be uptitrated at Month 3 if, in addition to no safety or tolerability concerns being identified, they meet strict laboratory criteria (total bilirubin ≤1.2 mg/dL, serum albumin ≥3.5 g/dL, INR <1.5, and platelet count >100,000/mm^3) at both baseline and all visits prior to Month 3. Furthermore, uptitrated subjects must continue to meet those criteria throughout the study to stay on the uptitrated dose; if at any time a subject exceeds these thresholds (including upon retesting),**	

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		they will be downtitrated to the lower OCA dose (10 mg).	
Section 7.1.2 Schedule of Study procedures Table 1 *And* Table 2 *And* Section 9.8 Visit Procedures	*Addition of Month 15 and Month 18 visits and procedures, EOT/EOS moved to Month 18* *Additional study visit days added to Pruritus VAS* [redacted] *"Other Metabolic Parameters" replaced with Insulin, C-Peptide, HOMA-β, and HOMA-IR, Month 2, Month 3, Month 4, Month 5, and Month 9 assessments removed.* *Free Fatty Acids assessment moved into separate row* *Footnotes edited* *Section 9.8 was updated to match Table 1 and Table 2*	*The following study visits were added to Table 1 Ver. 5:* **Month 15 and Month 18** *The following assessments were added to Table 1 Ver. 5:* Pruritus VAS: Day 1, Month 1, **Month 2,** Month 3,Month 4, **Month 5,** Month 6, **Month 9, Month 12, Month 15, Month 18,** and ET **Glucose and** HbA1c: SV1, Day 1, **Month 1, Month 2**, Month 3, **Month 4, Month 5**, Month 6, Month 9, **Month 12, Month 15**, Month 18, and ET **Insulin, C-Peptide, HOMA-β, and HOMA-IR:** Day 1, Month 1, Month 6, Month 12, Month 18, and ET **Free Fatty Acids: Day 1, Month 6, Month 12, Month 18, and ET** **HepQuant-SHUNT: Day 1, Month 3, Month 6, and Month 18** *The following footnotes were added in Table 1 Ver. 5:* **w. Blood samples will be collected at predose of cholate and 5, 20, 45, 60 and 90 minutes after administration of stable label cholate used to assess liver function in the HepQuant-SHUNT test.**	Given the onset of pruritus usually occurs within the first 6 months pruritus VAS will be assessed at every visit "Other metabolic parameters" was clarified and schedule of glucose testing was made to match HbA1c HepQuant Shunt was added as a substudy at US sites where capable Footnote for HepQuant-SHUNT procedure

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		Subjects enrolled at the selected US sites that are capable of administering the [redacted] test will participate in this mandatory assessment. The test should not be administered if the diastolic blood pressure is 110 mmHg or higher. The test can be rescheduled once the blood pressure is controlled. β-blockers, angiotensin II receptor blockers, or angiotensin-converting enzyme inhibitors should be delayed on the morning of testing until after the SHUNT test administration. *The following footnotes were edited in Table 1 Ver. 5:* [a] Screening Visit 2 must occur at least 4 weeks after Screening Visit 1 to confirm pretreatment serum chemistry levels, including ALT, AST, and **total** bilirubin. **Biopsy, EGD, ultrasound, TE, and MRE do not have to be performed on the same day as Screening Visit 1 or Screening Visit 2** [h] At Screening Visit 1, only AUDIT will be conducted. At D1, M6, M12**, M18**/EOT/EOS, and ET, all 3 assessments (AUDIT, smoking habit, and caffeine consumption) will be done. [m] Perform EGD procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with **endoscopic evidence of** varices will not be enrolled in the study. [p] All assessments, except for the post-dose collection of blood samples for the subjects participating in the PK **and/or** [redacted] must be completed prior to administration of investigational product. [r] ~~In the event any of the 2 ALT, AST, or total bilirubin assessments collected at Screening Visit 1 and~~	Edits for clarity

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		~~Screening Visit 2 differ by ≥30% and either lab value is >ULN, a third sample will be collected at an unscheduled visit as a confirmatory sample.~~ **In the event the Screening Visit 2 value for [redacted], or total bilirubin (conjugated bilirubin for subjects with an established diagnosis of Gilbert's syndrome) is ≥30% higher than the Screening Visit 1 value and > ULN, then a third measurement must be obtained at an unscheduled visit.** s. ~~Other metabolic parameters include fasting plasma glucose, insulin, C-peptide, HOMA-β, and HOMA-IR.~~ **Glucose only** [u] TE by Fibroscan® **and MRE** will be conducted at sites where device is available. Baseline TE should be performed once at Screening Visit 1, Screening Visit 2, or Day 1 (prior to first study drug administration). It is encouraged that TE is conducted prior to on-study liver biopsy(-ies). **MRE will be conducted only in subjects enrolled prior to Version 5 of the protocol who had baseline MRE and not in newly enrolled subjects.** *The following footnotes were edited in Table 2 Ver. 5:* [a] If the procedure indicated was performed at the end of the Double-Blind Phase, it is not necessary to repeat, unless the Investigator determines otherwise. **The day of the first dose from the OLE bottle is considered OLE Day 1. OLE visit windows are based on the OLE Day 1 Visit**	

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
		[g] Perform EGD procedure unless data from a recent EGD (within 6 months of OLE Day 1) are available. Subjects with **endoscopic** evidence of varices will not continue in the OLE Phase. [h] Subjects randomized to placebo during the Double-Blind Phase will be re-randomized to OCA 10 mg or OCA 10 mg → 25 mg arms on OLE Day 1; the placebo subjects in the OCA 10 mg → 25 mg arm will receive OCA 10 mg for 3 months followed by OCA 25 mg in the OLE **if the uptitration criteria are met (Section 9.2).** Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the treatment they were assigned. All assessments must be completed prior to administration of investigational product. **The first dose of OLE investigational product should be taken the day after the Month 18 assessments are completed.** [l] ~~Other metabolic parameters include fasting plasma glucose, insulin, C-peptide, HOMA-β, and HOMA-IR.~~ **Glucose only** *The following footnotes were removed from Table 2 Ver 5;* [n] ~~Whichever modality/ies used at Double-Blind Phase Baseline must be collected consistently at each OLE visit.~~	
Section 7.4.2 **Suspected** Drug Induced Liver Injury	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	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	Baseline calculations specified

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	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.	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. **Of note, the Baseline result is the average of results from Screening visits 1 and 2, Day 1, and any unscheduled visit which took place between Screening visit 1 and the Day 1 visit.**	
Table 3	*Criteria Resulting in Immediate Interruption of Investigational Product Upon First Observation added* *Footnote added*	**Conj. Bilirubin >ULN: ≥1.5x baseline: None** **[a] Baseline result is the average of results from Screening visits 1 and 2, Day 1, and any unscheduled visit which took place between Screening Visit 1 and the Day 1 Visit. This will remain the Baseline for the remainder of the study (including the OLE).**	Criteria added for subjects with baseline conjugated bilirubin >ULN Baseline calculations specified
Table 5	*Dose Downtitration Criteria added*	**Uptitrated subject no longer meets uptitration criteria: Downtitrate after confirmation by repeat testing (within 7 days): Not applicable**	To allow OCA 25 mg to a subset of subjects who meet additional specific criteria as outlined
Section 7.6 Investigational Product Dosage Interruption, Downtitration, Discontinuation, and	Investigational Product Dosage Interruption and Discontinuation Criteria	Investigational Product Dosage Interruption, **Downtitration**, Discontinuation, and **Rechallenge** Criteria	Edited to match Table 5

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Rechallenge Criteria			
Section 8.2.1 Other Reasons for Discontinuation	• Withdrawal of consent: – Consent may be fully withdrawn – Consent may be modified to discontinue study visits but allow semi-annual telephone contact	• Withdrawal of consent: – Consent may be fully withdrawn Consent may be modified to discontinue study visits but allow semi-annual telephone contact **of subject, subject's primary care physician, or personal contacts who can provide information on behalf of the subject by the Investigator**	Additional details added for follow-up of subjects given the extended study period
Section 8.2.1.1 Reasons for Subject Withdrawal from the HepQuant Substudy	*Addition of section*	**Subject Discontinuation** **In the event of an allergic or anaphylactic reaction to albumin, investigators must suspend administration of the cholates and manage the subject according to standard of care. Any subject with a hypersensitivity reaction to any component of the HepQuant-SHUNT kit will be withdrawn from the HepQuant substudy and will not undergo any further HepQuant procedure. Subjects that are withdrawn from the HepQuant-SHUNT substudy may continue in the study** [redacted]	[redacted]

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
		[redacted] **Circumstances that may warrant termination or suspension include, but are not limited to:** **• Determination of unexpected, significant, or unacceptable risk to participants** **• Demonstration of efficacy that would warrant stopping** **• Insufficient compliance to protocol requirements** **• Data that are not sufficiently complete and/or evaluable** **• Determination of futility** **Use of the kit in the study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and/or FDA.**	
Section 9.2.1 Double-Blind Phase	Subjects randomized to the OCA 10 mg → 25 mg arm in the Double-Blind Phase will receive OCA 10 mg for the first 3 months. ~~Uptitration to 25 mg may occur at Month 3, following review of individual subject safety and tolerability data.~~ Prior to the Month 3 study visit, the Medical Monitor will perform a review of consolidated safety data, including data	Subjects randomized to the OCA 10 mg → 25 mg arm in the Double-Blind Phase will receive OCA 10 mg for the first 3 months. Prior to the Month 3 study visit, the Medical Monitor will perform a subject-level consolidated review of safety data, including data from the Month 1 and 2 study visits, as well as that from any unscheduled visit(s), for	To allow uptitration to a subset of subjects who meet additional specific criteria as outlined

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	from the Month 1 and 2 study visits, as well as that from any unscheduled visit(s), for all study subjects. Case review and discussion with the Principal Investigator will occur as needed. ~~A subject may proceed with uptitration to OCA 25 mg (or matching placebo), if no safety and/or tolerability concerns are evident in the clinical judgement of the reviewer(s).~~ The review will include but not be limited to the following: • Liver-related adverse events • Safety laboratories: chemistry panel including glucose, hematology panel, coagulation parameters; computed MELD score and Child-Pugh score • Physical examination (development of clinically evident ascites or manifestations of hepatic encephalopathy) Additional considerations to determine the suitability to uptitrate will include an assessment of comorbid conditions, the subject's overall adverse event profile, concomitant medications with a focus on potentially hepatotoxic concomitant medications, and/or any new treatment(s) for comorbid condition(s). ~~The uptitration review process is detailed in the study-specific Medical Management Plan.~~ If uptitration at Month 3 is not feasible ~~due to special circumstances~~, the window for uptitration may be extended by up to one calendar month, after consultation and agreement with the Medical Monitor.	all study subjects. Case review and discussion with the Principal Investigator will occur as needed. The review will include but not be limited to the following: • Liver-related adverse events • Safety laboratories: chemistry panel including glucose, hematology panel, coagulation parameters; computed MELD score and CP score • Physical examination (development of clinically evident ascites or manifestations of hepatic encephalopathy) Additional considerations to determine the suitability to uptitrate will include an assessment of comorbid conditions, the subject's overall adverse event profile, concomitant medications with a focus on potentially hepatotoxic concomitant medications, and/or any new treatment(s) for comorbid condition(s). **A subject may be considered for uptitration to OCA 25 mg if no safety and/or tolerability concerns are evident in the clinical judgement of the reviewer(s).** If uptitration at Month 3 is not feasible, the window for uptitration may be extended by up to one calendar month, after consultation and agreement with the Medical Monitor. **The uptitration review process is detailed in the study-specific Medical Management Plan.**	

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	~~Subjects randomized to the OCA 10 mg or placebo arms will undergo dummy titration to maintain study blind.~~ ~~In addition, dosing frequency post-titration may be temporarily decreased for tolerability reasons, following discussions with the Medical Monitor. In addition, investigational product may be interrupted per safety criteria listed in Table 5 and Section 7.6. The procedures for re-initiating investigational product after prolonged interruption are provided in Section 8.2.2.~~	**Only those subjects who meet all of the following criteria will be eligible for uptitration at Month 3:** • **Total bilirubin ≤1.2 mg/dL, serum albumin ≥3.5 g/dL, INR <1.5, and platelet count >100,000/mm^3 at baseline, and at all visits prior to Month 3 (including any unscheduled visits).** • **Medical Monitor approval following a safety and tolerability assessment as described above.** **Subjects who do not meet these criteria will not be uptitrated for the remainder of the study.** **If at any time during the study, a subject who has undergone uptitration has total bilirubin >1.2 mg/dL, serum albumin <3.5 g/dL, INR ≥1.5, or platelet count ≤100,000/mm^3, the laboratory assessment(s) should be repeated within 7 days. If upon repeat evaluation, value(s) remain outside the specified criteria, investigational product should be downtitrated to a maximum daily dose of OCA 10 mg and the Medical Monitor should be notified promptly (see Table 5). Subjects randomized to the OCA 10 mg or placebo arms will undergo dummy titration to maintain study blind. All uptitration and downtitration will be implemented in a blinded fashion within IWRS to maintain the integrity of the study blind.**	

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
		Dosing frequency post-titration may be temporarily decreased for tolerability reasons, following discussions with the Medical Monitor. **In addition, investigational product may be interrupted per safety criteria listed in Table 5 and Section 7.6. The procedures for re-initiating investigational product after prolonged interruption are provided in Section 8.2.2.**	
Section 9.2.2 OLE Phase	Subjects who were randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg at entry into the OLE. Uptitration to OCA 25 mg at Month 3 in the OLE will ~~be conducted in the same manner applied in the Double-Blind Phase and described above.~~ Subjects randomized to OCA (10 mg or 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen. All dosing will be conducted in a ~~dummy titration fashion in order to maintain the blind~~ until all subjects complete the Double-Blind Phase and the database is locked.	Subjects who were randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg at entry into the OLE. Uptitration to OCA 25 mg at Month 3 in the OLE will **be determined based on the same criteria and assessments employed in the Double-Blind Phase and described above.** Subjects randomized to OCA (10 mg or 10 mg → 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen. All dosing, **uptitration, and downtitration** will be conducted in a **blinded fashion in order to maintain the integrity of the study blind** until all subjects complete the Double-Blind Phase and the database is locked.	Edited for clarity
Section 9.3 Concomitant Medications	Drugs with Potential NASH-modifying Properties Subjects should either not be taking any drugs with potential NASH-modifying properties (specifically,	Drugs with Potential NASH-modifying Properties Subjects should either not be taking any drugs with potential NASH-modifying properties (specifically, TZDs/glitazones, vitamin E, **or glucagon-like peptide -**	GLP-1 agonists added to list of potential NASH-modifiers

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	TZDs/glitazones ~~or~~ vitamin E) or be on a stable dose of these medications for 6 months before Day 1.	**1 agonists**) or be on a stable dose of these medications for 6 months before Day 1.	
Section 9.3.1 LDL-Lowering Medications	~~Statins~~ Given the prevalence of dyslipidemia in patients with NASH and the potential increase in total and LDL cholesterol following treatment with OCA, it is recommended that Investigators proactively monitor and manage lipid levels via appropriate medicinal interventions ~~(eg, statins)~~. Appendix A provides a general guidance for cholesterol management including monitoring, triggers for intervention, and treatment goals. Use of ~~statins~~ (eg, simvastatin, atorvastatin) should be at a stable dose ≥30 days before Day 1. During the study, changes ~~to statin doses or initiation of statin therapies~~ are allowed, given the potential increase in total and LDL cholesterol following treatment with OCA.	**LDL-Lowering Medications** Given the prevalence of dyslipidemia in patients with NASH and the potential increase in total and LDL cholesterol following treatment with OCA, it is recommended that Investigators proactively monitor and manage lipid levels via appropriate medicinal interventions. Appendix A provides a general guidance for cholesterol management including monitoring, triggers for intervention, and treatment goals. Use of **LDL-lowering medications** (eg, simvastatin, atorvastatin, **PCSK9 inhibitors**) should be at a stable dose ≥30 days before Day 1. During the study, changes to **LDL-lowering medication regimen** are allowed, given the potential increase in total and LDL cholesterol following treatment with OCA.	
Section 9.5.3 Emergency Unblinding Procedures	~~The DMC (refer to Section 16.13) will have access to the IWRS and will be able to unblind individual subjects.~~ The DMC will document details about any subject who was unblinded in the closed session DMC minutes, which will be made available to the Sponsor only after the double-blind database is locked and unblinded. Cases of premature unblinding (as noted above) will be reviewed by the DMC.	**The DMC (refer to Section 16.13) will have access to randomization and will be able to review the cases of premature unblinding.** The DMC will document details about any subject who was unblinded in the closed session DMC minutes, which will be made available to the Sponsor only after the double-blind database is locked and unblinded. Cases of premature unblinding (as noted above) will be reviewed by the DMC.	DMC access corrected

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Section 9.6.2 Subject Numbers	Subjects are assigned using a unique 10-character, 9-digit identifier (AAA-BBBCCC), independent of the randomization number. The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits represent the site number (BBB). The last 3 digits represent a unique screening number that is assigned in sequential order at each site starting with 001 (CCC).	Subjects are assigned using a unique 10-character, 9-digit identifier (AAA-BBBCCC), independent of the randomization number. The first 3 digits represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits represent the site number (BBB). The last 3 digits represent a unique screening number that is assigned in sequential order at each site starting with 001 (CCC). **Note, in the case of incorrect data entry by a site when more than one subject is inadvertently created, the spurious subject numbers will be deleted and may not be used again; in this circumstance there may be gaps in the subject numbering scheme at a site.**	Some sites may not have sequential numbering
Section 9.8 Visit Procedures *and* Table 2	Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. If Day 1 occurs on January 1st, Month 3 should ideally occur on April 1st (±1 week). This is the definition of a calendar month. The visit windows are listed in Table 1 and Table 2 . Acceptable windows for PK sampling timepoints are in Table 7	Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. **The day of the first dose from the OLE bottle is considered OLE Day 1. .** If Day 1 occurs on January 1st, Month 3 should ideally occur on April 1st (±1 week). This is the definition of a calendar month. The visit windows are listed in Table 1 and Table 2 2 . Acceptable windows for PK sampling timepoints are in Table 7	Edited for clarity
Section 9.8.3.1 Screening Visit 1	Perform EGD procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with varices will not be enrolled in the study.	Perform EGD procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with **endoscopic evidence of** varices will not be enrolled in the study.	Only endoscopic evidence of varices will be considered for exclusion

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Section 12.6.2 Noninvasive Panel of Liver Fibrosis Markers	FibroMeter (Echosens, Paris, France) combines multiple values including Fibroscan TE liver stiffness, age, gender, and blood-based biomarkers (platelets, alpha-2-macroglobulin, ALT, urea, ~~gamma-glutamyl transferase (~~GGT~~)~~, AST, ferritin, glucose level, ~~HA,~~ and prothrombin ratio) to quantify liver fibrosis. The test can be conducted by staff who are trained in the use and data interpretation of the diagnostic test. ~~FibroMax (BioPredictive, Paris, France) combines up-to-10 serum markers (alpha-2-macroglobulin, haptoglobin, apolipoprotein A-1, total bilirubin, GGT, ALT, AST, fasting glucose, triglycerides, and total cholesterol) with the age, sex, height, and weight of a subject to quantify liver fibrosis. The test can be performed by staff who are trained in the use and data interpretation of the diagnostic test.~~	FibroMeter (Echosens, Paris, France) combines multiple values including Fibroscan TE liver stiffness, age, gender, **weight,** and blood-based biomarkers (platelets, alpha-2-macroglobulin, ALT, urea, gamma- GGT, AST, ferritin, glucose level, and prothrombin ratio) to quantify liver fibrosis. The test can be conducted by staff who are trained in the use and data interpretation of the diagnostic test.	Weight is included as a value of the FibroMeter measurement Fibromax was removed as a marker
Section 13: Clinical Pharmacology Assessments	Subjects who receive at least one dose of OCA and have ~~bioanalytical~~ concentration data available will be included in the PK analysis. ~~Subjects with at least one 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.~~	Subjects who receive at least one dose of OCA and have **measurable plasma PK** concentration data available will be included in the PK analysis.	Edited for clarity
Section 13.1: Pharmacokinetic Blood Sampling	Subjects may opt to provide blood samples for serial PK assessments. ~~Serial blood samples will be used to characterize the PK at steady-state for a cohort of subjects at both OCA 10 mg and (when titrated) 25 mg doses. An~~	Subjects may opt to provide blood samples for serial PK assessments.	The plans no longer apply

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	~~assessment of steady-state exposures (on an aggregate level) will be performed by an internal Intercept clinical pharmacologist/pharmacometrician or designee who is discrete from the study team. These results may be made available to the DMC as appropriate (see Section 16.13).~~		
	Subjects participating in serial PK assessments will provide blood samples for measurement of OCA and its conjugates (glyco-OCA and tauro-OCA).	Subjects participating in serial PK assessments will provide blood samples for measurement of OCA and its conjugates (glyco-OCA and tauro-OCA) **at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post-dose on Month 1, Month 4, Month 12, and Month 18.**	Timing of PK assessments moved from lower paragraph
	Subjects will then receive a dose of investigational product with approximately 240 mL of water. ~~Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post-dose.~~ Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be provided following collection of the 1-hour PK sample; the meal will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 6-hour sample collection.	Subjects will then receive a dose of investigational product with approximately 240 mL of water. Subjects should not drink additional water for 1 hour after taking the dose of investigational product and will remain fasted until after the 1-hour sample is collected. A meal will be provided following collection of the 1-hour PK sample; the meal will be a meal replacement drink with nutrition information that has been submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 6-hour sample collection. Trough PK blood samples will be obtained **at Month 1, 3, 4, 6, 12, and 18** from all subjects.	

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	Trough PK blood samples will be obtained from all subjects. During the Double-Blind Phase: • Serial PK samples will be obtained at Month 1, Month 4, ~~and~~ Month 12 from subjects who agree to participate in the assessment. • Trough samples will be obtained from all subjects prior to dose administration at Months 1, 3, 4, 6, 12, and ET.	During the Double-Blind Phase: • Serial PK samples will be obtained at Month 1, Month 4, Month 12**, and Month 18** from subjects who agree to participate in the assessment. • Trough **PK blood** samples will be obtained from all subjects prior to dose administration at Months 1, 3, 4, 6, 12, **18,** and ET.	Updated due to the extension of the DB phase to 18 months
Section 14.3 HepQuant-SHUNT Assessments	*Addition of section*	**HepQuant-SHUNT Assessments** **An assessment of liver function using the HepQuant-SHUNT assessment will be performed as described in Table 1.** **Detailed instructions for HepQuant-SHUNT testing will be described in a study operational manual (HepQuant SHUNT Test Instructions for Use) that will be provided to sites offering this procedure in the US. For those US sites that participate in the mandatory HepQuant SHUNT sub-study, all subjects will be required to provide consent prior to participating. Failure of a subject to agree to participate in the sub-study will be a cause for screen-failure at these sites.** **In brief, the test involves placement of an indwelling peripheral venous catheter (usually in the antecubital**	[redacted]

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		vein of the arm), an injection of 20 mg 13C-cholate (cold, stable label, NOT RADIOACTIVE) intravenously and a drink of flavored solution of 40 mg d4-cholate (again, cold, stable label, NOT RADIOACTIVE), with 3 mL blood sampling at predose and 5, 20, 45, 60, 90 minutes post- [redacted]	

<table>
<tr><th>Section</th><th>Original Text (Version 4.0, 14 Jan 2019)</th><th>Revised Text (Version 5.0, 19 July 2019)</th><th>Key Change Reasons/ Justification for Change</th></tr>
<tr><td></td><td></td><td>[redacted]</td><td></td></tr>
<tr><td>Section 15.1.4: Relationship to Study Procedures
and
Table 10</td><td>Table 14: Relationship of Adverse Events to <s>Liver Biopsy and Other</s> Study Procedures
<table><tr><th>Relationship</th><th>Description</th></tr><tr><td>Related</td><td><s>A reaction that follows a reasonable temporal sequence from the required procedure (eg, liver biopsy); that follows a known or expected response pattern to the required study procedure.</s></td></tr><tr><td>Not Related</td><td>Any event that does not meet the above criteria.</td></tr></table></td><td>Table 15: Relationship of Adverse Events to Study Procedures
<table><tr><th>Relationship</th><th>Description</th></tr><tr><td>Related</td><td>A reaction that follows a reasonable temporal sequence from the HepQuant-SHUNT procedure or other study procedures; that follows a known or expected response pattern to the administration of cholate or collection of blood samples.</td></tr><tr><td>Not Related</td><td>Any event that does not meet the above criteria.</td></tr></table></td><td>HepQuant Shunt was added as a substudy at US sites where capable</td></tr>
<tr><td>Section 15.1.12</td><td>Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant</td><td>Pregnancies are not considered AEs in and of themselves; however, if a female study participant</td><td>Subjects may re-start treatment when they are no longer</td></tr>
</table>

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Pregnancy and Follow-up	while she is enrolled in the clinical study, she must ~~discontinue~~ investigational product immediately (Section 8.2.1.4) 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 downloading and completing the Pregnancy Report Form.	becomes pregnant while she is enrolled in the clinical study, she must **interrupt treatment with** investigational product immediately (Section 8.2.1.4) 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 downloading and completing the Pregnancy Report Form. **Any rechallenge of the investigational product should be implemented per the criteria outlined in Table 5.**	pregnant or breastfeeding
	The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor. The investigator should notify the Sponsor of the outcome of the pregnancy by completing Pregnancy Follow-up section in the EDC. In the situation that the EDC is no longer available due to study closure, ~~a~~ Pregnancy Outcome Form ~~should be completed~~ and faxed or emailed to the Sponsor. Thereafter, the subject and infant must be followed as considered appropriate by the Investigator and any new updates should be sent to the Sponsor.	The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor. The investigator should notify the Sponsor of the outcome of the pregnancy by completing Pregnancy Follow-up section in the EDC. In the situation that the EDC is no longer available due to study closure, **the outcome of the pregnancy should be added to the pregnancy resolution section of the downloaded** Pregnancy Outcome Form and faxed or emailed to the Sponsor. Thereafter, the subject and infant must be followed as considered appropriate by the Investigator and any new updates should be sent to the Sponsor.	Edited for clarity

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Section 15.2.6 Cardiovascular Risk Score *and* Section 8.2.2 Reinitiating Investigational Product After Interruption	Cardiovascular risk scores (~~Framingham Risk Score [~~FRS~~]~~, Reynolds score, and SCORE) will be calculated according to Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).	Cardiovascular risk scores (**10-year ASCVD Risk, FRS**, Reynolds score, and SCORE) will be calculated according to Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).	10-year ASCVD Risk was added to the markers of cardiovascular safety
Section 15.2.7 Laboratory Assessments	*Addition of paragraph*	**An assessment of steady-state exposures (on an aggregate level) will be performed by an internal Intercept clinical pharmacologist/pharmacometrician or designee who is discrete from the study team. These results may be made available to the DMC as appropriate (see Section 16.13).**	Edited for clarity
Section 16.1 Analysis Populations *and* Synopsis: Analysis Populations	• Intent-to-Treat (ITT) Population will include all randomized subjects ~~who receive at least 1 dose of investigational product (OCA or placebo)~~. The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.	Intent-to-Treat (ITT) Population will include all randomized subjects. The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment.	Edited for compliance with ICH guideline
Section 16.5.1 Other Histological Endpoints	*Addition of endpoints*	• **Changes in fibrosis score from Baseline to Month 18** • **Percentage of subjects with resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver**	Added to clarify analyses in line with SAP

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
		disease (simple or isolated steatosis) without steatohepatitis" as characterized/quantified by a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, at Month 18. • **Percentage of subjects with resolution of NASH based on overall pathologist interpretation (resolution of definite NASH) at Month 18.**	
Section 16.7 PD Analyses	PD assessments will be performed on FXR activation biomarkers (C4, FGF-19, and bile acids). ~~C4, FGF-19, and bile acids~~ will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The absolute change from Baseline and percent change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations before treatment.	PD assessments will be performed on FXR activation biomarkers (C4, FGF-19, and **plasma** bile acids**) and markers of inflammation, apoptosis and necrosis**. **PD assessments** will be summarized by treatment group using descriptive statistics at Baseline and at each on-study evaluation. The absolute change from Baseline and percent change from Baseline will also be summarized. Baseline is defined as the mean of all available evaluations before treatment.	Edited to include all PD assessments
Section 16.8 PK/PD Analysis	~~A sequential approach will be used to perform the population PK/PD analysis. The Bayesian estimates of individual PK parameters from the final population PK model will be used to generate PK profiles for each subject. The change in each PD assessment (eg, C4, FGF-19) over time will be incorporated into a maximum effect (E_{max}) model with OCA dose level as an independent variable. Estimated model parameters for each individual will be derived from prior E_{max}, and the half maximal effective~~	**The relationship between the PD markers and plasma exposure of OCA will be assessed. D**etails regarding the evaluation of PK/PD analyses to characterize exposure-response relationships in this NASH population will be specified in **the statistical analysis plan and/or a separate Clinical Pharmacology Analysis Plan** the clinical study report.	Details regarding the PK/PD analyses were removed and will be described in the statistical analysis plan and/or a clinical pharmacology analysis plan

Section	Original Text (Version 4.0, 14 Jan 2019)	Revised Text (Version 5.0, 19 July 2019)	Key Change Reasons/ Justification for Change
	~~concentration values, and baseline measures of each PD assessment. The appropriate structure of the variance-covariance matrix will also be evaluated. Fixed and random effect parameter estimates and associated asymptotic standard errors will be estimated. Descriptive statistics will be used to summarize Bayesian estimates of PK/PD parameters obtained from individual assessments in the population PK/PD model.~~ Further details regarding the evaluation of population PK and PK/PD analyses to characterize exposure-response relationships in this NASH population will be specified in a modeling and simulation plan. Results from these PK/PD analyses will be reported separate from the clinical study report.		
Section 20.3 Regulatory Documents	• Form FDA 1572	• Form FDA 1572 **(US only); in lieu of 1572 (for ex-US)**	Edited for clarity
Section 22 List of References	*References removed*		Removed due to removal of use within text

APPENDIX F. SUMMARY OF CHANGES: PROTOCOL VERSION 3.0 TO PROTOCOL VERSION 4.0 (DATED: 14 JAN 2019)

The revisions to Protocol 747-304 Version 4.0 summarized in this appendix include the following:

The text deleted from Protocol Version 3.0 is crossed out and revised text in Version 4.0 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 4.0 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 3.0, 05 Dec 2017)	Revised Text (Version 4.0, 14 Jan 2019)	Key Change Reasons/ Justification for Change
Study Personnel Contact Information	Primary Contact: [redacted] MBChB [redacted] ~~INC Research/~~ ~~inVentiv Health~~ ~~3201 Beechleaf Court,~~ ~~Suite 600~~ ~~Raleigh NC 27604~~ Email [redacted]	Primary Contact: [redacted] MB ChB [redacted] **Syneos Health** **1030 Sync Street** **Morrisville, NC 27560** Email: [redacted]	Change in study personnel contact information.
Synopsis, Investigators and/or Study Center(s)	Approximately ~~225~~ investigational sites, globally.	Approximately **300** investigational sites, globally.	The number of study sites has been increased to meet enrollment goals for this study.
Synopsis, Inclusion Criteria	3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Effective methods of contraception are listed below:	3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). **Female subjects are considered as being of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.**	Updated definition of woman of childbearing potential.

Synopsis, Exclusion Criteria	18. Evidence of other known forms of chronic liver disease including: – Positive test result at Screening for hepatitis B surface antigen – Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA test result – Primary biliary ~~cirrhosis~~, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome – Alcoholic liver disease – Wilson disease, hemochromatosis, or iron overload – Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion) – Prior known drug-induced liver injury within 5 years before Day 1 – Known or suspected HCC 31. Concurrent participation in any other interventional ~~or noninterventional~~ clinical trial.	18. Evidence of other known forms of chronic liver disease including: – Positive test result at Screening for hepatitis B surface antigen – Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or **confirmed** history of **a** positive HCV RNA test result**(s)** – Primary biliary **cholangitis**, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome – Alcoholic liver disease – Wilson disease, hemochromatosis, or iron overload – Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion) – Prior known drug-induced liver injury within 5 years before Day 1 – Known or suspected HCC 31. Concurrent participation in any other interventional clinical trial.	Changes were made for clarification purposes (exclusion criterion #18). Change was made for clarification that subjects will not be excluded for participating in noninterventional clinical trials (exclusion criterion #31).

<table>
<tr>
<td>7.4.2, Drug-Induced Liver Injury</td>
<td>
Table 3: Liver Laboratory Criteria for Monitoring for Suspected Hepatic Injury or Decompensation
<table>
<tr><td colspan="3">Criteria Resulting in Immediate Interruption of Investigational Product Upon First Observation</td></tr>
<tr><td>Baseline</td><td>Upper Laboratory Threshold</td><td>Frequency of Monitoring (Repeat Test)</td></tr>
<tr><td rowspan="2">Conj. bilirubin ≤ULN</td><td>≥1.5x ULN</td><td><s>NA</s></td></tr>
<tr><td>If <s>T</s>otal <s>B</s>ili <s>rise</s> ≥0.5 mg/dL, <s>reassess</s> conjugated <s>if</s> >ULN</td><td><s>NA</s></td></tr>
<tr><td>Creatinine</td><td>>ULN AND increase by 20%</td><td><s>NA</s></td></tr>
</table>
<s>NA=not applicable</s>
</td>
<td>
Table 3: Liver Laboratory Criteria for Monitoring for Suspected Hepatic Injury or Decompensation
<table>
<tr><td colspan="3">Criteria Resulting in Immediate Interruption of Investigational Product Upon First Observation</td></tr>
<tr><td>Baseline</td><td>Upper Laboratory Threshold</td><td>Frequency of Monitoring (Repeat Test)</td></tr>
<tr><td rowspan="3">Conj. bilirubin ≤ULN</td><td>≥1.5x ULN</td><td>None</td></tr>
<tr><td>If total bilirubin increases by ≥0.5 mg/dL from baseline and conjugated bilirubin is >ULN</td><td>None</td></tr>
<tr><td>Creatinine</td><td>>ULN AND increase by 20% from baseline</td><td>None</td></tr>
</table>
</td>
<td>Changes were made for clarification and consistency purposes.</td>
</tr>
</table>

7.4.3.1. Child-Pugh Assessment

Table 4: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum total bilirubin	µmol/L	<~~35~~	~~35~~-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

Table 4: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum total 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**ne**	Grade 1 or 2	Grade 3 or 4

Changes were made for clarification and consistency purposes.

7.5, Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis	NA (new section added, **Medical Management of Subjects with Symptomatic Cholelithiasis and/or Cholecystitis**)	**NASH is associated with several known risk factors for cholelithiasis, such as obesity, type 2 diabetes, and other metabolic abnormalities. The prevalence of gallstone disease in NASH is higher than in the general population. The majority of gallstones are asymptomatic and may never become symptomatic.** **Because symptomatic events of cholelithiasis and/or cholecystitis may develop in subjects with or without a known history of gallstones, it is important that all subjects be (1) monitored for signs and symptoms suggestive of gallstone disease and (2) counseled to recognize and seek immediate medical attention if they experience symptoms suggestive of cholelithiasis and/or cholecystitis.** **If a subject experiences symptoms suggestive of cholelithiasis and/or cholecystitis, s/he 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, IP should be interrupted (see Section 7.6).**	The Sponsor is implementing new rules for implementing and monitoring of IP in cases of symptomatic cholelithiasis and/or cholestasis.

<table>
<tr>
<td>7.6, Investigational Product Adjustment, Interruption, and Discontinuation Criteria</td>
<td>New language added.</td>
<td>Investigational product should not be interrupted in the following instances: 1) in subjects who previously experienced an event of symptomatic cholelithiasis and/or cholecystitis, and in whom symptoms have fully resolved at the present time while on IP; 2) in subjects who experience an event that is not symptomatic (such as an incidental finding of gallstones during an ultrasound exam); or 3) in subjects who have already undergone a cholecystectomy following a prior event of cholelithiasis or cholecystitis (and who have no symptoms suggestive of retained or recurrent bile duct stones).
The following row was added to Table 5:
<table>
<tr>
<td>Symptomatic cholelithiasis and/or cholecystitis</td>
<td>Interrupt</td>
<td>Subjects who meet the requirements for IP interruption for symptomatic cholelithiasis and/or cholecystitis may not resume IP until approval from the Medical Monitor is received or further guidance from the Sponsor i Subjects should remain in the study and complete all protocol-specified assessments, as defined in Table 1, while off IP. In subjects undergoing cholecystectomy following an event of cholelithiasis or cholecystitis, IP may be resumed after the procedure, provided there are no signs symptoms suggestive of retained or recurrent bile duct stones.</td>
</tr>
</table>
</td>
<td>The Sponsor is implementing new rules for implementing and monitoring of IP in cases of symptomatic cholelithiasis and/or cholestasis.</td>
</tr>
</table>

8.1, Subject Population	This study will be conducted at approximately ~~225~~ international study sites with experience in treating patients with compensated cirrhosis due to NASH. Prospective subjects will be identified primarily from the hospital and/or physician's database of patients with NASH or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international NASH patient societies, forums, or networks.	This study will be conducted at approximately **300** international study sites with experience in treating patients with compensated cirrhosis due to NASH. Prospective subjects will be identified primarily from the hospital and/or physician's database of patients with NASH or may be referred from other physicians. Subjects may self-refer to an Investigator if they become aware of the study through local, national, or international NASH patient societies, forums, or networks.	The number of study sites has been increased to meet enrollment goals for this study.
8.1.1, Subject Inclusion Criteria	3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Effective methods of contraception are listed below:	3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). **Female subjects are considered as being of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal, 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However ,in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.**	Updated definition of woman of childbearing potential.

8.1.2, Subject Exclusion Criteria	18. Evidence of other known forms of chronic liver disease including: – Positive test result at Screening for hepatitis B surface antigen – Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA test result – PBC, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome – Alcoholic liver disease – Wilson disease, hemochromatosis, or iron overload – Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion) – Prior known drug-induced liver injury within 5 years before Day 1 – Known or suspected HCC 31. Concurrent participation in any other interventional ~~or noninterventional~~ clinical trial.	18. Evidence of other known forms of chronic liver disease including: – Positive test result at Screening for hepatitis B surface antigen – Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or **confirmed** history of **a** positive HCV RNA test result**(s)** – PBC, primary sclerosing cholangitis, autoimmune hepatitis, or overlap syndrome – Alcoholic liver disease – Wilson disease, hemochromatosis, or iron overload – Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level below the lower limit of normal or exclusion at the Investigator's discretion) – Prior known drug-induced liver injury within 5 years before Day 1 – Known or suspected HCC 31. Concurrent participation in any other interventional clinical trial.	Changes were made for clarification purposes (exclusion criterion #18). Change was made for clarification that subjects will not be excluded for participating in noninterventional clinical trials (exclusion criterion #31).

9.8.12, OLE Months 2, 3, 4, 5, 9	• Calculations will be performed by the Sponsor or designee for: – MELD Score – CP Score/Class (assessment of ascites and hepatic encephalopathy is required) – Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI) – Noninvasive panel of liver fibrosis (ELF, FibroMax, and Fibrometer) (Month ~~9~~ only) – DILI management algorithm (liver biochemistry)	• Calculations will be performed by the Sponsor or designee for: – MELD Score – CP Score/Class (assessment of ascites and hepatic encephalopathy is required) – Noninvasive scores of liver fibrosis (NFS, FIB-4, and APRI) – Noninvasive panel of liver fibrosis (ELF, FibroMax, and Fibrometer) (Month **3** only) – DILI management algorithm (liver biochemistry)	Correction of error.
15.1.10, Follow-Up of AEs and SAEs	New paragraph added to section.	**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.**	The Sponsor is implementing new rules for implementing and monitoring of IP in cases of symptomatic cholelithiasis and/or cholestasis.
15.2.3, Vital Signs	Vital signs will be assessed at the visits as specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase): ~~oral~~ temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes. 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.	Vital signs will be assessed at the visits as specified in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase): temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes. 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.	Change was made for clarification purposes.

APPENDIX E. SUMMARY OF CHANGES: PROTOCOL VERSION 2.0 TO PROTOCOL VERSION 3.0 (DATED: 05 DEC 2017)

The previous version of this protocol (747-304 Version 2.0, 17 May 2017) was amended to create Version 3.0 on 05 Dec 2017. Key updates made to the protocol Version 2 are summarized below:

1. The **study design** has been updated as follows: Subjects who meet the entry requirements will be randomized in a 1:1:1 ratio to one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or placebo, in conjunction with local standard of care.
2. The primary efficacy endpoint has been changed to improvement in fibrosis **AND no worsening of Nonalcoholic Steatohepatitis (NASH).**
3. Subjects with a diagnosis of **cryptogenic cirrhosis** and presence of metabolic risk factor are no longer eligible to enroll in the study.
4. The Introduction was revised to highlight the need for **close monitoring specifically for patients who progress to have clinical evidence of hepatic decompensation and other complications due to advanced cirrhosis**. Reference is made to sections describing specific criteria for investigational product adjustment, interruption, or discontinuation based on adverse events or laboratory values. This language also emphasizes the need for careful observation and evaluation of the entire clinical picture over and above system-generated alerts and flags for lab values. The importance of continued monitoring and appropriate referrals are highlighted in the event of potential diagnostic dilemmas and mandate follow-up until such dilemmas are stabilized.
5. Guidance was added that subjects should be instructed to contact the site promptly upon awareness of **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 the whites of eyes, and bruising easily.
6. Guidance was added that the Investigator should contact the study Medical Monitor upon awareness when any signs and symptoms of hepatic decompensation are observed in any subject.
7. **Pancreatitis**. Subjects who are diagnosed with pancreatitis or develop symptoms consistent with pancreatitis, will be monitored for 3 months after the onset of symptoms per standard of care, including amylase and lipase enzyme levels.
8. The **visit windows for the 2 screening visits** are clarified to allow for sufficient time to complete screening procedures.
9. The **gallbladder** ultrasound will be performed at Screening to obtain baseline status.
10. Subjects with known evidence of **varices** or with **MELD score >12** will not be enrolled in the study.
11. The **duration of OLE phase** is changed from 24 months to 12 months.

12. **SF-36, microbiome/metabolome assessments, and genetic analyses** have been removed.

The text deleted from Protocol Version 2.0 is crossed out and revised text in Version 3.0 is indicated in bold font in the table below. Minor changes including typos or editorial revisions are not listed individually in the summary table below.

<table>
<tr><th>Section</th><th>Original Text (Version 2.0, 17 May 2017)</th><th>Revised Text (Version 3.0, 05 Dec 2017)</th><th>Key Change
Reasons/Justification for Change</th></tr>
<tr><td>Title Page</td><td>Added Study Name (Acronym)</td><td>The REVERSE Study
<u>R</u>andomized phase 3 study <u>EV</u>aluating the Efficacy and safety of obeticholic acid in subjects with compensated ci<u>R</u>rhosis due to nonalcoholic St<u>E</u>atohepatitis</td><td>To help the study sites, Investigators, and subjects in referencing the study easily during verbal or written communications</td></tr>
<tr><td>Study Personnel Contact Information</td><td>[redacted]PhD
[redacted]Clinical Development

<table><tr><td>Primary Contact:</td><td>[redacted]MD
[redacted]~~Drug Safety~~
~~Intercept~~ Pharmaceuticals, Inc.
~~(Intercept)~~</td></tr><tr><td>Telephone:</td><td>[redacted]</td></tr><tr><td>Email:</td><td>[redacted]</td></tr></table>
~~Safety~~ ~~Contact~~ Information</td><td>[redacted]PhD
[redacted]Clinical Development

<table><tr><td>Primary Contact:</td><td>[redacted]MBChB
[redacted]Drug Safety
INC Research/inVentiv Health
3201 Beechleaf Court, Suite 600
Raleigh NC 27604</td></tr><tr><td>Telephone:</td><td>[redacted]</td></tr><tr><td>Email:</td><td>[redacted]</td></tr></table>
<table><tr><td>Secondary Contact:</td><td>[redacted]MD
[redacted]
Intercept Pharmaceuticals, Inc.</td></tr><tr><td>Email:</td><td>[redacted]</td></tr></table>
SAE Reporting Information</td><td>Updated Sponsor information

Change of personnel</td></tr>
</table>

Synopsis, Investigators and/or Study Center(s), *and* Section 8.1, Subject Population	Approximately ~~150~~ investigational sites, globally. This study will be conducted at approximately ~~150~~ international study sites with experience in treating patients with compensated cirrhosis due to NASH.	Approximately **225** investigational sites, globally. This study will be conducted at approximately **225** international study sites with experience in treating patients with compensated cirrhosis due to NASH.	Number of study sites have been increased to meet enrollment goals for this study.
Synopsis, Studied Period Synopsis, Duration of the Treatment *and* Section 7.1.3, Study Duration	The maximum duration of individual subject participation for this study is approximately ~~3~~ years and ~~2~~ months, including a Screening Period of up to ~~8~~ weeks, a 1-year Double-Blind Phase, and an optional Open-Label Extension (OLE) expected to last approximately ~~2~~ years. The maximum duration of treatment is approximately ~~3~~ years including a 1-year Double-Blind Phase, and an optional OLE expected to last approximately ~~2~~ year~~s~~.	The maximum duration of individual subject participation for this study is approximately **2** years and **3** months, including a Screening Period of up to **12** weeks, a 1-year Double-Blind Phase, and an optional Open-Label Extension (OLE) expected to last approximately **1** year. The maximum duration of treatment is approximately **2** years including a 1-year Double-Blind Phase, and an optional OLE expected to last approximately **1** year.	The screening period has been increased from 8 weeks to 12 weeks to provide sufficient time for screening procedures. The OLE Phase has been decreased to 1 year.
Synopsis, Primary Objectives. *and* Section 6.1 Primary Objectives	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage ~~using the~~ Nonalcoholic Steatohepatitis (NASH) Clinical Research Network (CRN) scoring system from Baseline to Month 12 ~~• Safety and tolerability~~	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage **with no worsening of** Nonalcoholic Steatohepatitis (NASH) **defined as no increase in hepatocellular ballooning or lobular inflammation, using the NASH** Clinical Research Network (CRN) scoring system, from Baseline to Month 12	The primary efficacy endpoint has changed to include no worsening of NASH in addition to fibrosis improvement. "Safety and tolerability" is now one of the secondary objectives of the study

Synopsis, Secondary Objectives. *and* Section 6.2 Secondary Objectives	• Histological changes in fibrosis including improvement, no worsening, and progression from Baseline to Month 12 using the following criteria, as appropriate:	• Histological changes in fibrosis including **(1)** improvement, **(2)** no worsening, and **(3)** progression from Baseline to Month 12 using the following criteria, as appropriate: **• Resolution of NASH defined as overall histopathological interpretation of 1) "no fatty liver disease" or 2) "fatty liver disease (simple or isolated steatosis) without steatohepatitis" AND a nonalcoholic fatty liver disease (NAFLD) activity score (NAS) of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to Month 12** **• Histological improvement in fibrosis by at least 1 stage and improvement in NAS by at least 2 points with at least 1 point improvement each for hepatocellular ballooning and lobular inflammation, using the NASH CRN scoring system, from Baseline to Month 12** **• Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning), using the NASH CRN scoring system, from Baseline to Month 12**	Clarification. Changes in histological parameters of fibrosis will be individually assessed. Additional secondary objectives added to the study that are relevant to the population being studied.
	• Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint): - Death (all cause) - Liver transplant ~~(if model for end-stage liver disease [MELD] <15 at Baseline)~~ - MELD score ≥15 ~~(if MELD ≤12 at Baseline)~~	• Occurrence of all-cause mortality and liver-related clinical outcomes for the following adjudicated events (clinical outcomes composite endpoint): - Death (all cause**s**) - Liver transplant - MELD score ≥15	This objective was updated since subjects with MELD score >12 are excluded from the study.
	• The effect of OCA treatment compared to placebo on the following additional measures and markers: – Health-related quality of life	• The effect of OCA treatment compared to placebo on the following additional measures and markers: – Health-related quality of life **(eg, patient reported outcomes)**	Clarifications

	- ~~Hepatic function~~ as assessed by MELD and CP scores	- **Disease progression** as assessed by MELD and CP scores • **Safety and tolerability**	

Synopsis, Methodology. *and* Section 7.1, Overall Study Design	~~Up to approximately 30% of total enrolled subjects may have a diagnosis of cryptogenic cirrhosis and presence of metabolic risk factor.~~ Subjects who progress to CP Class B or Class C during the study will discontinue investigational product, but ~~should be encouraged to continue study visits.~~ **Double-Blind Phase (12 Months):** Subjects will be screened for a period of up to ~~8~~ weeks before entering the study. Subjects who meet the entry requirements will be randomized in a 1:1 ratio to ~~receive~~ placebo ~~or OCA daily~~ in conjunction with ~~local~~ standard of care. ~~Subjects will receive OCA 10 mg for the first 3 months. At Month 3, all subjects will titrate to OCA 25 mg once daily unless there are safety concerns.~~ Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment ~~(yes or no) and by cryptogenic cirrhosis~~ (yes or no). **Open Label Extension (up to ~~24~~ Months)**: Subjects who complete the Double-Blind Month 12 Visit are eligible to enroll into the OLE ~~for the evaluation of safety~~. All subjects will receive OCA upon entry into the OLE. Subjects ~~who received~~ placebo ~~during~~ the Double-Blind Phase will ~~receive OCA 10 mg daily for 3 months and titrate to OCA 25 mg daily in the same manner that was applied during the Double-Blind Phase. Subjects who received OCA during the Double-Blind phase will~~ continue the same dosing regimen they received at the end of the Double-Blind Phase.	Subjects who progress to CP Class B or Class C during the study will discontinue investigational product, but **are expected to be followed through to study closure (or at the discretion of the Sponsor).** **Double-Blind Phase (12 Months):** Subjects will be screened for a period of up to **12** weeks before entering the study. Subjects who meet the entry requirements will be randomized in a 1:1**:1** ratio to **one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or** placebo, in conjunction with **the** standard of care**. Uptitration will be determined based on the safety and tolerability assessments completed prior to Month 3**. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). **Open Label Extension (up to 12 Months)**: Subjects who complete the Double-Blind Month 12 Visit **(and continue to receive investigational product)** are eligible to enroll into the OLE. All subjects will receive OCA upon entry into the OLE. Subjects **randomized to** placebo **in the Double-Blind Phase** will **be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg (ie, OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg at OLE Month 3). Uptitration will be based on the safety and tolerability assessments completed prior to Month 3. Subjects randomized to OCA (10 mg or 25 mg dose)** during the Double-Blind Phase will continue the same dosing regimen they received at	Subjects with cryptogenic cirrhosis will not be enrolled under Version 3 of the protocol. The new study design includes 3 treatment arms. Clarification of OCA treatment assignment during OLE Phase for subjects who were randomized to placebo arm during the Double-Blind Phase.

		the end of the Double-Blind Phase**; however, they will undergo dummy titration to maintain study blind until all subjects complete the Double-Blind Phase and the database is locked.** *Note: In Section 7.1, hyperlink to Section 9.2 is also included for the titration scheme at Month 3 (Double-Blind Phase) or at OLE Month 3.*	
Synopsis, Study Design Diagram *and* Section 7.1.1, Study Design Diagram	*The study diagram was updated per changes in study design*	*Diagram was updated as follows:* – *Change from 2 groups (Placebo, and OCA 10 mg) to 3 groups (Placebo, and OCA 10 mg, and OCA 10 mg→25mg) during the Double-Blind Phase.* – *1:1 randomization at D1 changed to 1:1:1 randomization* – *Screening period: "≤8 weeks" changed to "≤1 weeks"* – *Change in OLE from "up to 2 years" to "up to 1 year".*	Clarifications

Synopsis, Study Design Diagram - Footnotes *and* Section 7.1.1, Study Design Diagram - Footnotes	CP = Child Pugh; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = Once Daily. Note: Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH ~~or cryptogenic cirrhosis with metabolic factors assumed to be due to NASH~~ will be enrolled in the study. Subjects with CP Class B or CP Class C cirrhosis are excluded. • a Two screening visit assessments will be performed ~~at least 4 weeks apart~~. Screening Visit 1 will occur ~~8~~ weeks prior to Day 1, and Screening Visit 2 will occur 4 weeks ~~± 2 days prior to Day 1.~~ Subjects without a liver biopsy obtained ≤12 months prior to Day 1 ~~will~~ have a biopsy ~~at Screening Visit 2~~. b ~~During the double-blind period, all subjects will titrate to OCA 25 mg (or matching placebo) at Month 3 unless safety concerns dictate otherwise. A blinded review of Month 1 and Month 2 safety data, including liver biochemistry and adverse events by the medical monitor will be conducted prior to a subject's Month 3 visit.~~ c ~~All subjects who enroll into the OLE will receive OCA.~~ Subjects ~~randomized to~~ placebo in the Double-Blind Phase will ~~initiate investigational product of~~ OCA 10mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg. ~~Uptitration will be based on safety and tolerability assessments completed at Month 1, Month 2, and Month 3 of the OLE.~~ Subjects ~~randomized to OCA~~ will continue the same dosing regimen they received at the end of the Double-Blind Phase. d The study will remain blinded until all subjects complete the Double-Blind Phase. To maintain	CP = Child Pugh; **CRN = clinical research network;** NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; OLE = open-label extension; QD = once daily. **a All subjects will receive OCA upon entry into the OLE.** **b During the OLE period, subjects will return for site visits at Months 1, 2, 3, 4, 5, 6, 9, and 12.** Note**s**: • Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH **(determined by central reading of liver histology)** will be enrolled in the study. Subjects with **hepatic decompensation** or CP Class B or CP Class C cirrhosis are excluded. • Two screening visit assessments will be performed. Screening Visit 1 will occur **no more than 12** weeks prior to Day 1, and Screening Visit 2 will occur **at least 4 weeks after Screening Visit 1.** • Subjects without a liver biopsy obtained ≤12 months prior to Day 1 **must** have a biopsy **completed during the screening period**. • **Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no).** • Subjects **who received** placebo **during** the Double-Blind Phase will **be re randomized to either** OCA 10 **mg or OCA 10 mg → 25 mg (ie, OCA 10 mg** for the first 3 months of the OLE prior to uptitrating to OCA 25 mg **at OLE Month 3).** Subjects **who received OCA during the Double-Blind Phase** will continue the same dosing regimen they received at the end of the Double-Blind Phase. • The study will remain blinded until all subjects complete the Double-Blind Phase **and the**	Clarifications

	blinding, all placebo, ~~OCA 10 mg~~, and OCA ~~25 mg~~ tablets and bottles will be identical~~. Once all subjects have titrated to the 25 mg dose in the OLE, subjects may receive investigational product with an open-label identifying the product as OCA 25 mg~~.	**database is locked.** To maintain blinding, all **investigational product** (placebo and OCA) tablets and bottles will be identical.	
Synopsis, Number of Subjects (Planned) *and* Section 7.2, Number of Subjects	Approximately ~~360~~ subjects will be enrolled in the study.	Approximately **540** subjects will be enrolled in the study.	Number of subjects have been increased to meet the goal of sufficiently powered primary objective of the study.

Synopsis, Inclusion Criteria *and* Section 8.1.1, Subject Inclusion Criteria	2. Subjects with confirmed diagnosis of NASH ~~with~~ a fibrosis score of 4 based ~~on~~ NASH CRN scoring system determined by central reading of a liver biopsy obtained no more than 12 months before Day 1, ~~OR~~ ~~Subjects with cryptogenic cirrhosis assumed to be due to NASH as determined by central reading of a liver biopsy obtained no more than 12 months before Day 1 accompanied by TWO of the following risk factors~~ ~~- Obesity (body mass index ≥30 kg/m2)~~ ~~- Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test, or random plasma glucose ≥200 mg/dL) or on any prescription glucose-lowering agent for Type 2 diabetes~~ ~~- Abdominal obesity (waist circumference >102 cm [>40 in] for men and >88 cm [>35 in] for women) with no evidence of ascites by imaging unless obvious on physical exam~~ ~~- Dyslipidemia (triglyceridemia ≥150 mg/dL and low high-density lipoprotein [<40 mg/dL in men and <50 mg/dL in women]) or using a prescription lipid-lowering medication due to dyslipidemia~~ 3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Effective methods of contraception are ~~considered to be those~~ listed below:	2. Subjects with **a** confirmed diagnosis of NASH **and** a fibrosis score of 4 based **upon the** NASH CRN scoring system determined by central reading of a liver biopsy obtained no more than 12 months before Day 1. 3. Contraception: Female subjects of childbearing potential must use ≥1 effective method (≤1% failure rate) of contraception during the study until 4 weeks following the last dose of investigational product (including OLE doses). Effective methods of contraception are listed below:	Subjects with cryptogenic cirrhosis will not be enrolled under Version3 of the protocol. Editorial

Synopsis, Exclusion Criteria *and* Section 8.1.2, Subject Exclusion Criteria	~~8~~.Total bilirubin >2 mg/dL (subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >2 mg/dL if their conjugated (direct) bilirubin is <2× ULN) ~~9~~. Albumin <~~3.2~~ g/dL ~~28.~~ Previous exposure to OCA within 12 months	**For alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin for which if Screening Visit 1 and Visit 2 values differ by ≥30% and either of the lab values is > upper limit of normal (ULN), then a third sample will be collected at an unscheduled visit as a confirmatory sample.** **3.MELD score >12** 5.Documented presence of varices based on prior endoscopy performed within 6 months of Day 1 **10**. Total bilirubin >2 mg/dL (subjects with **an established diagnosis of** Gilbert's syndrome **and a normal hemoglobin and reticulocyte count** may be enrolled despite a total bilirubin level >2 mg/dL if their conjugated (direct) bilirubin is <2× ULN) **11. Conjugated bilirubin ≥1.5x ULN** **12**. Albumin <**3.5** g/dL **22. LDL cholesterol <50 mg/dL (irrespective of statin use)** **28. Chronic use (≥12 months) of drugs historically associated with drug-induced NAFLD within the 5 years before Day 1 (eg, amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins).** **31. Concurrent participation in any other interventional or noninterventional clinical trial.** **33**. Previous exposure to OCA within 12 months **of Day 1** *Note: Exclusion criteria 28 in main protocol (Section 8.1.2) also refers to Section 9.3* **28. Chronic use (≥12 months) of drugs historically associated with drug-induced**	Clarification Additional exclusion criteria are added to the protocol as follows: Subjects with MELD >12, presence of varices, conjugated bilirubin ≥1.5x ULN, low LDL cholesterol, or chronic use of drugs historically associated with drug-induced NAFLD will not be enrolled in the study. Other criteria have been clarified as indicated

		NAFLD within the 5 years before Day 1 (eg, amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins; see Section 9.3).	
Synopsis, Liver Histology and Event Adjudication and Data Monitoring Committee Oversight and Section 16.14, Adjudication Committees	Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN scoring system, ~~or cryptogenic cirrhosis with metabolic factors assumed to be due to NASH~~ must be confirmed for study eligibility. All suspected liver-related clinical outcomes, and major adverse cardiovascular events (MACE)~~,~~ ~~and drug-related hepatic injury events~~ that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The ~~3~~ committees ~~and event types they~~ are responsible for adjudicating events are as follows:. ~~• Hepatic Safety Committee: Adjudicates all suspected drug-related hepatic injury events~~ The DMC will include hepatologists, pharmaceutical physicians, epidemiology/ cardiology expert(s), and statistician(s); they will not be involved in the study as Investigators, adjudication committee members, or consultants. All members will have considerable experience with clinical study conduct and DMCs ~~before joining the DMC~~.	Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN scoring system must be confirmed for study eligibility. All suspected liver-related clinical outcomes, **and** major adverse cardiovascular events (MACE), and drug-related hepatic injury events that occur after administration of the first dose of investigational product will be reviewed by the following blinded adjudication committees, depending on event type, before inclusion in any analysis. The **2** committees **that** are responsible for adjudicating events are as follows: The DMC will include hepatologists, pharmaceutical physicians, epidemiology/ cardiology expert(s), **drug-induced liver injury (DILI) expert(s)** and statistician(s); they will not be involved in the study as Investigators, adjudication committee members, or consultants. All members will have considerable experience with clinical study conduct and DMCs	Subjects with cryptogenic cirrhosis will not be enrolled under Version 3 of the protocol. Clarification Clarification

Synopsis, Criteria for Evaluation *and* Section 11, Overview of Assessments	**Analysis Variable**	**Endpoint Assessments**	Endpoint Assessments have been updated per changes in the study objectives.
	Primary Objectives		
	Histological improvement in fibrosis using NASH CRN scoring system	Improvement in fibrosis by at least 1 stage, using NASH CRN scoring system, from Baseline to Month 12	
	~~Safety and tolerability~~	~~TEAEs, SAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes), and pruritus VAS~~	
	Secondary Objectives		
	Clinical outcomes	Occurrence of any of the following adjudicated events: death (all cause); liver transplant ~~(if MELD <15 at Baseline);~~ HCC confirmed by 2 complementary imaging modalities unless already confirmed by biopsy; MELD score ≥15 ~~(if MELD < at Baseline)~~;	
	Metabolic parameters	Glucose, insulin, C-peptide, HbA1c, HOMA-IR	
	Health-related quality of life	CLDQ-NAFLD, EQ-5D-5L, WPAI~~, and SF-36~~	
	Noninvasive assessments of liver disease assessed by serum markers and imaging tests	Noninvasive radiological liver fibrosis measurements (conducted at sites where device is available): TE by Fibroscan®, ~~LiverMultiScan™~~, and MRE	
	PD of OCA on FXR activation	C4, FGF-19, and bile acids	
	Analysis Variable	**Endpoint Assessments**	SF-36, and LiverMultiScan, assessments have been removed from the study
	Primary Objectives		
	Histological improvement in fibrosis using NASH CRN scoring system	Improvement in fibrosis by at least 1 stage **with no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation,** using NASH CRN scoring system, from Baseline to Month 12	
	Secondary Objectives		
	Resolution of NASH	**No fatty liver disease or fatty liver disease (simple or isolated steatosis) without steatohepatitis AND a NAS of 0 for ballooning and 0-1 for inflammation, using the NASH CRN scoring system, from Baseline to Month 12**	
	Histological improvement in fibrosis and NAS	**Improvement in fibrosis by at least 1 stage and improvement in NAS by at least 2 points with at least 1-point improvement each for hepatocellular ballooning and lobular inflammation, using the NASH CRN scoring system, from Baseline to Month 12**	
	Improvement in histological features of NASH	**Improvement in steatosis by at least 1 point using NASH CRN scoring system, from Baseline to Month 12**	

	Additional Secondary Objectives Assessed at the End of the OLE				
	OLE safety and tolerability	TEAEs, ECGs, vital signs, and clinical laboratory assessments (including lipid profile changes)			
	Efficacy	~~All~~ efficacy assessments conducted in the Double-Blind Phase will be repeated in the OLE Phase			
				Improvement in lobular inflammation by at least 1 point using NASH CRN scoring system, from Baseline to Month 12	
				Improvement in hepatocellular ballooning by at least 1 point using NASH CRN scoring system, from Baseline to Month 12	
			Clinical outcomes	Occurrence of any of the following adjudicated events: death (all cause); liver transplant; HCC confirmed by 2 complementary imaging modalities unless already confirmed by biopsy; MELD score ≥15	
			Metabolic parameters	Glucose, insulin, C-peptide, HbA1c, **HOMA-β,** HOMA-IR	
			Health-related quality of life	CLDQ-NAFLD, EQ-5D-5L, **and** WPAI	
			Noninvasive assessments of liver disease assessed by serum markers and imaging tests	Noninvasive radiological liver fibrosis measurements (conducted where device is available): TE by Fibroscan®, **and/or** MRE	
			PD of OCA on FXR activation	C4, FGF-19, **plasma** bile acids	
			Safety and tolerability	**TEAEs, adverse events of special interest (including pruritus and hepatic safety), ECGs, vital signs, pruritus VAS, and clinical laboratory assessments**	

			(including lipid profile changes)		
		Additional Secondary Objectives Assessed at the End of the OLE			
		OLE safety and tolerability	TEAEs, **adverse events of special interest (including pruritus and hepatic safety),** ECGs, vital signs, **pruritus VAS**, and clinical laboratory assessments (including lipid profile changes)		
		Efficacy	**A subset of** efficacy assessments conducted in the Double-Blind Phase will be repeated in the OLE Phase		

Synopsis, Statistical Methods (and subsections) *and* Section 16.12.1, Safety Analyses (OLE)	~~A total of approximately 360~~ subjects will be enrolled and randomized into the study in a 1:1 ratio to placebo ~~or OCA~~. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no) ~~and cryptogenic cirrhosis (yes or no)~~. The mITT Population will include all ITT subjects who dose titrate ~~at Month 3 per protocol~~. Primary and key secondary efficacy hypothesis testing will be based on the ITT population. ~~Exploratory~~ analyses of the primary endpoint will be conducted using the mITT and PP population. The primary efficacy analysis will test the following hypotheses: • H~~0~~: The percentage of subjects with fibrosis improvement by at least 1 stage ~~using~~ the NASH CRN ~~score~~ from Baseline to Month 12 is equal between placebo and OCA. • H~~1~~: The percentage of subjects with fibrosis improvement by at least 1 stage using NASH CRN ~~score~~ from Baseline to Month 12 is different between placebo and OCA.	**PK/PD analytical methods will be detailed in a separate modeling and simulations plan, and all results will be documented separate from the clinical study report.** **Approximately 540** subjects will be enrolled and randomized into the study in a 1:1**:1** ratio to **OCA 10 mg, OCA 10 mg → 25 mg, or** placebo **arms**. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). The mITT Population will include all ITT subjects **except those** who **are not eligible to** dose titrate **due to safety or tolerability reasons**. Primary and key secondary efficacy hypothesis testing will be based on the ITT population. **Supportive** analyses of the primary endpoint will be conducted using the mITT and PP population. The primary efficacy analysis will test the following hypotheses: • H_{01}: The percentage of subjects with fibrosis improvement by at least 1 stage **and no increase in hepatocellular ballooning or lobular inflammation** using the NASH CRN **scoring system** from Baseline to Month 12 is equal betweenplacebo and OCA **10 to 25 mg titration**. • H_{11}: The percentage of subjects with fibrosis improvement by at least 1 stage **and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation, using the** NASH CRN scoring system, from Baseline to Month 12 is different between placebo and OCA **10 to 25 mg titration**. • **H_{02}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular**	Clarification Number of subjects have been increased to sufficiently power the study Clarification Clarification

		inflammation, using the NASH CRN score from Baseline to Month 12 is equal between placebo and OCA 10 mg. **• H_{12}: The percentage of subjects with fibrosis improvement by at least 1 stage and no worsening of NASH defined as no increase in hepatocellular ballooning or lobular inflammation, using the NASH CRN score from Baseline to Month 12 is different between placebo and OCA 10 mg.**	
	The hypothesis testing of the ~~primary and~~ key secondary endpoint will be conducted in a sequential closed testing gate-keeping procedure. For the comparison of the primary and key secondary efficacy endpoints, a Cochran–Mantel–Haenszel test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] ~~and cryptogenic cirrhosis [yes/no])~~ will be used. ~~Additional secondary endpoints will be analyzed; however, statistical testing will be considered descriptive and exploratory only.~~	The hypothesis testing of **the** key secondary endpoint will be conducted in a sequential closed testing gate-keeping procedure. For the comparison of the primary and key secondary efficacy endpoints, a Cochran–Mantel–Haenszel **(CMH)** test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] will be used. **Analyses of the clinical outcomes composite endpoint and individual components of outcome events will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo, as listed under the secondary objectives. Only adjudicated events will be included in analyses. Subjects with none of these events will be censored at the date of last contact. For the analysis of time to first occurrence of adjudicated events, in addition to the CMH test statistics, a log rank test stratified by the randomization stratification factor will be used. Kaplan-Meier estimates of the distribution of the time-to-event will be tabulated and graphed by treatment group.**	Clarifications Clarification
	Safety Analyses Safety evaluations will comprise treatment-emergent AEs, ~~adjudicated CV events,~~ vital signs, electrocardiograms (ECGs), and clinical laboratory results.	Safety Analyses Safety evaluations will comprise treatment-emergent AEs, **AEs of special interest including pruritus and hepatic safety, adjudicated cardiovascular events** vital signs,	

	Pharmacokinetic/Pharmacodynamic Analyses The change in each PD assessment (eg, C4, FGF-19) over time will be incorporated into a maximum effect (Emax) model with OCA as an independent variable. Safety Analyses (OLE) ~~Similar analyses to that which are described~~ will also conducted for the OLE. ~~Efficacy Analyses (OLE)~~ ~~Efficacy analyses conducted during the Double-Blind Phase will be repeated during the OLE. Separate summaries will be presented by the randomized treatment assignment in the double-blind phase. For subjects with optional biopsy in OLE, histological changes will be assessed.~~	electrocardiograms (ECGs), and clinical laboratory results. Pharmacokinetic/Pharmacodynamic Analyses The change in each PD assessment (eg, C4, FGF-19) over time will be incorporated into a maximum effect (Emax) model with OCA **dose level** as an independent variable. **These PK/PD analyses will be reported in a separate document outside of the clinical study report.** Safety Analyses (OLE) **Safety evaluations conducted during the Double-Blind Phase** will **also** be conducted for the OLE.	
Synopsis, Statistical Methods Sample Size Justification *and* Section 16.2, Determination of Sample Size	A sample size of 180 subjects per group with an assumed 5% discontinuation rate will provide 90% power to demonstrate a statistically significant treatment difference between OCA and placebo group based on Chi square test with 2-sided type I error at 0.01 level, ~~assuming~~ a responder rate of 23% and 8% in the OCA and placebo groups, respectively, based on data from literature, observed effect size on fibrosis improvement in advanced fibrosis subjects in FLINT and practical consideration.	A sample size of 180 subjects per group with an assumed 5% discontinuation rate will provide 90% power to demonstrate a statistically significant treatment difference between OCA **25 mg** and placebo group based on Chi square test with 2-sided type I error at 0.01 level, assuming. **This assumes** a responder rate of 23% and 8% in the OCA and placebo groups, respectively, based on data from literature, observed effect size on fibrosis improvement in advanced fibrosis subjects **in the Farnesoid X receptor Ligand OCA in Nonalcoholic Steatohepatitis Treatment (**FLINT**) study** and practical consideration.	Editorial
Section 5.1, Overview of Nonalcoholic Steatohepatitis and Obeticholic Acid	For patients with NASH without diabetes, practice guidelines from the American Association for the Study of Liver Diseases recommend the use of vitamin E as first line therapy.	For patients with NASH without diabetes, practice guidelines from the American Association for the Study of Liver Diseases recommend the use of vitamin E as first line therapy **(Chalasani 2012).**	Clarification

Section 5.3, Clinical Experience with Obeticholic Acid	OCA is under investigation for the treatment of multiple chronic liver diseases, including the treatment of NASH, primary biliary ~~cirrhosis~~ (PBC, also called primary biliary ~~cholangitis~~ [Beuers 2015a, Beuers 2015b, Beuers 2015c]), primary sclerosing cholangitis, biliary atresia, and other chronic liver diseases. ~~In May 2016,~~ the United States ~~(US)~~ Food and Drug Administration (FDA) ~~has granted accelerated approval for OCA (Ocaliva) for the treatment of PBC. In December~~ 2016, the European ~~Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) approved conditional marketing authorization for~~ Ocaliva for the treatment of PBC. The clinical development program for OCA in subjects with NAFLD or NASH includes data from the following ~~3~~ completed studies:	OCA is under investigation for the treatment of multiple chronic liver diseases, including the treatment of NASH, primary biliary **cholangitis** (PBC, also called primary biliary **cirrhosis**) [Beuers 2015a, Beuers 2015b, Beuers 2015c]), primary sclerosing cholangitis, biliary atresia, and other chronic liver diseases. **OCA was granted accelerated approval by** the United States Food and Drug Administration (FDA) **on 27 May 2016. Conditional approvals were obtained on 12 Dec** 2016 **in** the European **Union (EU), and by Health Canada on 24 May 2017 under the trademark** Ocaliva for the treatment of PBC **in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA**. The clinical development program for OCA in subjects with NAFLD or NASH includes data from the following **4** completed studies: **• Double-Blind Phase of Study 747-209: A Phase 2, double-blind, randomized, placebo-controlled, multicenter study evaluating the effect of OCA, and the subsequent addition of statin therapy, on lipoprotein metabolism in subjects with NASH with fibrosis stage 1 to 4, but no evidence of hepatic decompensation.** **Study 747-209 enrolled subjects with histological evidence of definite or probable NASH confirmed by liver biopsy and a nonalcoholic fatty liver disease activity score (NAS) of 4 or greater, randomized in a 1:1:1:1 ratio to receive OCA 5 mg, OCA 10 mg, OCA 25 mg or placebo, orally once daily, for 16 weeks. Randomization was stratified by LDL concentration (fasting serum low-density lipoprotein (LDL) cholesterol at Screening Visit 2; ≤125 mg/dL or >125 mg/dL) and baseline fibrosis stage (stage 1, 2 or stage 3, 4). Statin-free subjects as well as**	Updated OCA approval information Updated information regarding OCA clinical development program

	In addition, ~~2~~ studies evaluating OCA for the treatment of NASH are currently ongoing: ~~• A Phase 2, double-blind, randomized, placebo-controlled study (Study 747-209) evaluating the effect of OCA and atorvastatin treatment on lipoprotein metabolism in subjects with NASH~~	**statin-treated subjects (following a 4-week statin washout) were eligible for enrollment. All subjects initiated treatment with atorvastatin at a dose of 10 mg once daily after 4 weeks of OCA treatment. After 4 weeks of 10 mg atorvastatin treatment, dosing was increased to 20 mg once daily, and continued for an additional 4 weeks. After 4 weeks of treatment at 20 mg daily dose, atorvastatin dosing could be titrated up or down as clinically indicated.** **A total of 84 subjects were randomized into the study, with baseline cirrhosis status being pre cirrhotic in 62 (74%) subjects and cirrhotic in 22 (26%) subjects. Seventy-nine (94%) subjects completed the Double-Blind phase. An increase in LDL cholesterol was observed following treatment with OCA and the addition of low-dose atorvastatin (10 mg) reversed OCA-associated changes in LDL cholesterol back to baseline levels and lower within 4 weeks.** **Three subjects discontinued due to AEs: 1 subject on OCA 5 mg for Stage 4 breast cancer, and 2 subjects on OCA 25 mg for pruritus.** In addition, **the following** studies evaluating OCA for the treatment of NASH are currently ongoing: • **The open label extension portion of Study 747-209.**	

Section 5.4.1, Rationale for Study Design	The incidence of NASH is increasing and NASH is likely to be the leading cause of liver transplant by 2020, highlighting the need for development of effective therapies that may improve steatohepatitis and ~~resulting~~ fibrosis, potentially delaying liver transplant or death. Thus, Study 747 304 will evaluate efficacy and safety of OCA in subjects with NASH with cirrhosis (defined by a NASH Clinical Research Network [CRN] score of 4), with the exception of subjects with Child Pugh (CP) score ≥7.	The incidence of NASH is increasing and NASH is likely to be the leading cause of liver transplant by 2020, highlighting the need for development of effective therapies that may improve steatohepatitis and fibrosis, potentially delaying liver transplant or death. Thus, Study 747 304 will evaluate efficacy and safety of OCA in subjects with **histological evidence of** NASH with cirrhosis (defined by a NASH Clinical Research Network [CRN] score of 4), with the exception of subjects with **hepatic decompensation or** Child Pugh (CP) score ≥7.	Clarification
Section 5.4.3, Rationale for Obeticholic Acid Doses and Duration	~~Subjects~~ will be ~~randomized to receive~~ OCA 10 mg ~~or placebo~~ daily for the ~~first 3 months then titrate to OCA 25 mg or placebo daily for the~~ duration of ~~the Double-Blind Phase~~. This dose titration was selected based the known mechanism of FXR and on clinical experience in completed Phase 2 studies in subjects with NAFLD (747-203) and NASH (FLINT) as well as a clinical pharmacology study in subjects with hepatic impairment (Study 747-103). Guidelines for subjects who progress beyond CP Class A are provided in Section ~~7.5~~.	**In addition to placebo, two dosing regimens of OCA** will be **evaluated in this study: (1) Titration regimen (**OCA 10 mg → **25 mg) in which OCA will be initiated at a dose of 10 mg once daily followed by uptitration to 25 mg once daily at Month 3; and (2) OCA 10 mg once** daily for the **entire** duration of the **study**. This dose titration was selected based **upon** the known mechanism of FXR and on clinical experience in completed Phase 2 studies in subjects with NAFLD (747-203) and NASH (FLINT), as well as a clinical pharmacology study in subjects with hepatic impairment (Study 747-103). **Study 747-209 evaluated a range of doses from 5 mg to 25 mg in subjects with NASH and fibrosis, including subjects with compensated cirrhosis. In this study, treatment of NASH subjects with compensated cirrhosis with up to 25 mg OCA was found to be safe and well tolerated, and the AE profile of cirrhotic subjects was not different from that of precirrhotic subjects.** Guidelines for subjects who progress beyond CP Class A are provided in Section **7.4**.	Rationale for the changes in the study design is described.

Section 5.5, Summary of Known Potential Risks with Investigational Product		**The rate of progression and risk of hepatic decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk. Investigators should inform participating subjects of known and anticipated risks associated with OCA treatment and prompt them to communicate with the Investigators in the event of any adverse experiences.** **Post-Marketing Cases of Liver Injury in PBC** **Liver injury, liver decompensation, liver failure, and death have been reported in patients with moderate to severe hepatic impairment (Child-Pugh B and C) when Ocaliva was dosed more frequently than recommended in labeling for such patients (up to 7 times the recommended dose). In addition, serious liver adverse events have been reported in the post-marketing setting in OCA-treated patients without cirrhosis or with mild liver impairment, both early in treatment and after months of treatment.** **Signs and symptoms reported in patients experiencing liver-related adverse outcomes who received Ocaliva include: increases in bilirubin and other liver enzymes, new or worsening pruritus, new or worsening fatigue, vague neuropsychiatric symptoms (such as dysphoria), abdominal pain, nausea, vomiting, diarrhea, dehydration, jaundice, and liver decompensation.** **Clinical Study Experience** **Liver-related events** **Systemic and hepatic concentrations of OCA increase significantly in patients with moderate to severe hepatic impairment. In PBC clinical studies, a dose response relationship was observed for the occurrence of liver related adverse reactions with OCA, including jaundice, worsening ascites, and primary biliary**	

		cholangitis flare with dosages of OCA 10 mg to 50 mg once daily. Most events occurred at a dose up to 5 fold higher (50 mg) than the maximum recommended marketed dose (10 mg). **Clinically relevant increases in AST, ALT, or conjugated bilirubin (markers of liver injury) were rarely seen at the intended clinical doses of 5 mg or 10 mg. Elevated liver enzymes were observed in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies; however, these elevations were only considered to be of clinical concern at the maximum dose of 250 mg daily. Cases of hepatic decompensation cases have also occurred in PBC. The majority of the cases were considered not related or unlikely related to investigational product by the Investigator. In general, subjects who experienced hepatic decompensation either entered the study with more advanced disease, or for those studies where subjects started earlier in disease progression, events of hepatic decompensation generally occurred at least 1 year after the initiation of treatment or on higher doses.** **Four cases of hepatic decompensation and potential drug induced liver injury (DILI) in the PBC program assessed as possibly related were examined by an independent hepatic adjudication committee. Although the subjects experienced progression of liver dysfunction while on OCA treatment, the committee concluded the pattern was consistent with progression of underlying disease rather than a DILI event.** **Analyses of liver-related safety information from NASH subjects treated with OCA demonstrate an overall hepatic safety profile consistent with PBC. There is no evidence to indicate a consistent, dose-dependent worsening of liver**	

		biochemistries at doses up to 25 mg, including ALT, AST or bilirubin. Modest increases in ALP levels have occurred following treatment with OCA, however levels were generally within upper limits of normal. ALP elevations are generally not associated with a rise in GGT, suggesting that these changes are unlikely to be due to cholestatic liver injury. **The incidence of liver-related adverse events in NASH clinical studies overall was low. Events specifically reflective of hepatic decompensation in the NASH program was low with comparable incidence between OCA and placebo (2% OCA versus % placebo).** **Two cases of hepatic decompensation have been reported as SUSARs, 1 of which resulted in death. In the ongoing Phase 3 clinical Study 747-303, a NASH subject with no evidence of cirrhosis at baseline presented with acute liver injury, acute kidney injury, hyperbilirubinemia, and a generalized vesicular rash, which required hospitalization. The Investigator assessed the events as severe, serious due to hospitalization, important medical events, and possibly related to the investigational product (remains blinded). In the ongoing Phase 2 open-label extension phase of Study 747-209, a NASH subject with a history of NASH cirrhosis with hepatic impairment and presumptive evidence of portal hypertension reported events of severe diarrhea, jaundice, and unintended weight loss (30 lbs in approximately 1 month) approximately 5 months after initiating treatment with OCA 25 mg; OCA was discontinued at that time. The subject was subsequently hospitalized for acute renal failure and died due to renal failure and liver failure leading to cardiac arrest. The Investigator assessed both the event of acute renal failure and the event of liver failure as fatal**	

		in severity, serious, and unlikely related to investigational product. **Pruritus** **Pruritus is an expected adverse event associated with OCA, particularly in subjects with cholestatic liver diseases such as PBC where pruritus is a common symptom of the disease. In PBC clinical studies, the incidence of pruritus was 68% for OCA-treated subjects compared with 40% in placebo-treated subjects. The majority of events have been reported as mild to moderate in severity and infrequently resulted in early discontinuation. The majority of subject's experiencing pruritus did not require an intervention for pruritus. The incidence and severity of pruritus have been shown to be dose dependent, but there is no evidence of association with stage or progression of underlying disease. In NASH clinical trials, AEs of pruritus was reported less frequently with OCA treatment relative to PBC. In the FLINT study, mild to moderate pruritus occurred in 23% of OCA-treated subjects compared with 6% of placebo-treated subjects and only 1 subject discontinued therapy as a result of pruritus.** **Lipids** **In subjects with NASH (FLINT), compared to placebo, treatment with OCA was associated with statistically significant elevations in the mean total serum cholesterol and low-density lipoprotein (LDL) levels, and a decrease in the mean HDL, which remained within normal limits. These changes developed within the first 12-week time point after beginning of treatment, decreased over time after Week 12, and returned to baseline levels when OCA treatment was withdrawn.**	

		Withdrawal of OCA treatment reversed the OCA-induced LDL increase in all groups, including subjects who were not on statins (Neuschwander-Tetri 2015a). In Study 747-209, subjects with NASH and dyslipidemia received placebo or OCA 5mg, 10 mg, and 25 mg once daily, for up to 4 weeks. Subjects then initiated concurrent treatment with 10 mg atorvastatin once daily titrated to 20 mg once daily based on tolerability. At Week 4, subjects experienced approximately 20% to 25% increases in LDL-C particles across all OCA groups. By Week 8, atorvastatin treatment effectively lowered LDL-C to below baseline levels across all OCA groups compared to patients not on a statin. **Together, the small magnitude of OCA mediated cholesterol and LDL changes, coupled with their reversibility upon cessation of OCA treatment and/or responsiveness to statin-initiation, suggest that this risk can be managed by statins as needed.** **An independent data monitoring committee (DMC) has performed detailed reviews of several studies including the Phase 3, clinical outcomes study in PBC (747-302) and the Phase 3, pivotal study in NASH with fibrosis (747-303). The DMC reviewed data (unmasked for PBC and unblinded by treatment group for NASH with a total of approximately 1000 subjects) in closed sessions, which excluded participation of the Sponsor. Based on these reviews, the DMC recommended that both studies continue without modification providing further support for the lack of safety concern and positive benefit-risk profile of OCA.** **In summary, based on the robust efficacy of OCA observed in PBC and NASH clinical studies, including improvements in liver biochemistry, fibrosis, and key histological**	

		features of NASH, as well as the overall safety profile of OCA (in >2300 healthy subjects and subjects with chronic liver diseases), the benefit-risk profile is favorable.	
Section 5.6, Importance of Monitoring of Disease Progression	*This is a new section added to Version 3.*	**NASH is a chronic, progressive liver disease; therefore, it is important that subjects with NASH are closely monitored to ensure early identification of potential disease progression to cirrhosis, decompensation and/or liver injury. The rate of progression and risk of decompensation is variable and may be rapid in certain patients necessitating closer surveillance of patients at risk. Therefore, more extensive safety monitoring and appropriate dosing adjustments, interruptions, and discontinuations will be implemented to improve subject oversight and safety. Investigators together with the Sponsor's Medical Monitor or designee will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules based laboratory monitoring.** **Subjects will be monitored for potential hepatic injury and/or progression to decompensation (Section 7.4). Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 7.5 and Section 7.6. The more extensive monitoring is important given the elevated risk of decompensation and potential for higher hepatic exposure to OCA in this population.**	Additional safety procedure added to the protocol

Section 7.1.2, Table 1, Schedule of Study Procedures (Double-Blind Phase)	*The following study visit windows were changed*: • Screening Visit 1: ~~8~~ Weeks prior to Day 1 • Screening Visit 2: 4 Weeks ~~prior to Day 1 ±2 days~~ • Day 1: ~~±1 wk~~ • Mth 12/EOT/EOS: ±~~1~~ wk *The following assessments were removed from Ver.3* • ~~LiverMultiScan~~ • ~~Microbiome/Metabolome Stool Sample Analysis (All US Subjects)~~ • ~~Blood Samples for Genetic Analysis~~ *The following timepoints were removed from Ver.3* • Lipoprotein analysis: ~~SV1, M1, M2, M3, M4, M5, and M9~~ • Thyroid hormones: ~~SV1~~ • TE and MRE: ~~M3, and M9~~ • Trough PK: ~~M2, and M5~~	*The following study visit windows were changed*: • Screening Visit 1: **≤12** Weeks prior to Day 1 • Screening Visit 2: ≥4 **after SV1** • Day 1: **≤12 Weeks after SV1** • Mth 12/EOT/EOS: -**2** wk *The following assessments were added to Ver. 3:* • **Waist and hip circumference: All visits except at SV1** • **Vital signs: All visits except at SV2** • **Assess signs and symptoms of hepatic injury or decompensation: All visits except screening visits** • **Gallbladder assessment: at SV1, D1, M6, and M12** • **EGD Procedure: SV1** • **Review DILI management algorithm (liver biochemistry): All visits except SV1, SV2, and D1** *The following assessments were added to Ver. 3:* • Liver biopsy (optional): **ET** • Pruritus VAS: **M3** • Thyroid hormones: **D1**	Clarification (study visits windows, vital assessments) Gallbladder assessment: Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/ pancreatic complications) EGD procedure added for screening for varices LiverMultiScan, and Micobiome/Metabolome: These changes are based on the feasibility of conducting these procedure at study sites.

Section 7.1.2, Table 1, Schedule of Study Procedures, (Double-Blind Phase), FOOTNOTES	a ~~The 2~~ Screening ~~Visits~~ must occur at least 4 weeks ~~apart~~ to confirm pretreatment serum chemistry levels, including ALT and AST. e Prior medications taken within ~~6~~ months of Day 1 are to be recorded at Screening Visits 1 and 2, and Day 1 only. For all other visits, only concomitant medications are to be recorded. f ~~Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes.~~ Height will be measured at Screening visit 1 only. BMI and waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurements. **h** ~~AUDIT only at~~ Screening Visit 1. ~~j~~ Hepatobiliary ultrasound for HCC screening at Screening ~~is~~ not required if data from a recent historic ultrasound (within 3 months of ~~screening~~) are available. ~~k If hepatobiliary ultrasound for HCC screening~~ was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound. ~~l Including assessment of ascites and hepatic encephalopathy.~~ ~~m~~ On-study liver biopsies should be performed after the hepatobiliary ultrasound for HCC screening. Liver biopsy procedure ~~at Screening Visit 2~~ is not required for subjects who have had a biopsy ≤12 months prior to randomization (Day 1) and can provide unstained slides. ~~n Optional procedure. If a biopsy was obtained within 12 months of Day 1, subjects do not need to undergo this procedure.~~	a Screening **Visit 2** must occur at least 4 weeks **after Screening Visit 1** to confirm pretreatment serum chemistry levels, including ALT, AST, **and bilirubin.** e Prior medications taken within **12** months of Day 1 are to be recorded at Screening **Visits 1 and 2**, and Day 1 only. For all other visits, only concomitant medications are to be recorded. f Height will be measured at Screening Visit 1 only. **The calculations for** BMI and waist-to-hip ratio will be calculated performed via EDC**: BMI from weight and height measurements, and waist-to-hip ratio** from waist and hip circumference measurements. g **Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes**. **h At** Screening Visit 1**, only AUDIT will be conducted. At D1, M6, M12/EOT/EOS, and ET, all 3 assessments (AUDIT, smoking habit, and caffeine consumption) will be done**. **k** Hepatobiliary ultrasound for HCC screening **and gallbladder assessments** at Screening **are** not required if data from a recent historic ultrasound (within 3 **calendar** months of Day 1) are available. **l Ultrasound will be conducted to enhance HCC surveillance and for gallbladder assessment. If ultrasound** was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound. **m Perform EGD procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with varices will not be enrolled in the study.** **n** On-study liver biopsies should be performed after the hepatobiliary ultrasound for HCC screening. Liver biopsy procedure is not required for subjects	Version 3 footnotes “a”, “e”, “g”, “h”, “n”, “o”, “r”, “s”, “t”) Clarifications. (Version 3 footnotes “k” & “l”) Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications) (Version 3 footnote “o”) Screening for varices, an exclusionary criterion.

	o Health-related quality of life (EQ-5D-5L, CLDQ-NAFLD, WPAI, ~~and SF-36~~), and standardized generic measure of health status for the assessment of health utilities (eg, hospitalization [reason, length of stay, major medical procedures], emergency room visits, outpatient physician visits, concomitant medications. r In the event ~~either~~ of the 2 ALT or AST assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample will be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility. s Other metabolic parameters include fasting plasma glucose, insulin, C-peptide, and HOMA-IR. t Urine β-hCG pregnancy tests must be performed for females of childbearing potential before entry. If positive, a confirmatory blood test must be performed. If the blood test is also positive, the subject may not be enrolled in the study. u ~~Sceening~~ TE~~, LiverMultiScan~~, and MRE can be performed at ~~either~~ Screening Visit 1 ~~or~~ Screening Visit ~~2. Baseline TE, LiverMultiScan, and MRE should be conducted~~ prior to ~~an~~ on-study liver biopsy. ~~Whichever modality/ies used at baseline must be collected consistently at each visit.~~ w Serial PK blood samples will be obtained ~~0.5 hour prior to dosing and~~ at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose. ~~x Subjects will be permitted to decline to provide a blood sample for the genetics study without affecting their involvement in the study. Only~~	who have had a biopsy ≤12 months prior to randomization (Day 1) and can provide unstained slides **for central reading. Liver biopsy at ET is an optional procedure.** o Health-related quality of life (EQ-5D-5L, CLDQ-NAFLD, **and** WPAI), and standardized generic measure of health status for the assessment of health utilities (eg, hospitalization [reason, length of stay, major medical procedures], emergency room visits, outpatient physician visits, concomitant medications). r In the event **any** of the 2 ALT, AST, or **total bilirubin** assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30% **and either lab value is >ULN**, a third sample will be collected at an unscheduled visit as a confirmatory sample. s Other metabolic parameters include fasting plasma glucose, insulin, C-peptide, **HOMA-β,** and HOMA-IR. t Urine β-hCG pregnancy tests must be performed for females of childbearing potential before entry. If positive, a confirmatory blood test must be performed. If the blood test is also positive, the subject may not be enrolled in the study**, and if already enrolled, must be discontinued immediately**. u TE **by Fibroscan®** and MRE **will be conducted at sites where device is available. Baseline TE should be** performed **once** at Screening Visit 1, Screening Visit **2, or Day 1** (prior to **first study drug administration). It is encouraged that TE is conducted prior to** on-study liver biopsy(-ies). w Serial PK blood samples will be obtained at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours postdose.	(Version 3 footnote "p") SF-36 procedure will not be conducted. (Version 3 footnote "u") LiverMultiScan will not be conducted.

	~~RNA samples will be collected at Month 12/EOS/EOT and ET.~~		
Section 7.1.2, Table 2, Schedule of Study Procedures (OLE Phase)	*The following study visit windows was changed*: • Day 1 (Month 12 DB): ±~~1~~ wk *The following study visits were removed from Ver.3* • Study Visits M15, M18, M21, and M24 *The following assessments were removed from Ver.3* • ~~LiverMultiScan and MRE~~ • ~~Serum markers of inflammation, apoptosis, and necrosis~~ • ~~PD blood samples~~ • ~~Trough PK blood samples~~ • ~~Serial PK blood samples~~ • ~~Blood samples for genetic analysis~~ • ~~Exploratory markers of disease severity~~ *The following timepoints were removed from Ver.3* • Lipoprotein analysis: ~~M1, M3, M4, AND M6~~	**Note: Only those subjects who complete the Double-Blind Month 12 Visit and continue to receive investigational product are eligible to enroll into the OLE.** *The following study visit windows was changed*: • Day 1 (Month 12 DB): **-2** wk *The following assessments were added to Ver. 3:* • **Waist and hip circumference: All timepoints** • **Vital signs: All timepoints** • **Assess Signs and Symptoms of Hepatic Injury or Decompensation: All timepoints** • **EGD Procedure: D1 (M12 DB)** • **Review DILI management algorithm (liver biochemistry): All timepoints** *The following timepoints were added to Ver. 3:* • Physical exam: **M12/EOT,/EOS, and ET** • 12-lead electrocardiogram: **M12/EOT,/EOS, and ET** • AUDIT: **ET** • HCC Screening: **ET** • Liver biopsy: **M12/EOT,/EOS, and ET** • Urinalysis: **M12/EOT,/EOS** Clarification: • CP Score/Class **(assessment of ascites and HE is required)**	Clarification OLE Phase has been decreased from 2 years to 1 year Several assessments have been scaled back due to changed scope of the OLE Phase. Clarifications

Section 7.1.2, Table 2, Schedule of Study Procedures (OLE Phase), FOOTNOTES	~~d~~ Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes. ~~Height will be measured at Screening only.~~ BMI and waist-to-hip ratio will be calculated via EDC from waist and hip circumference measurements. ~~f Including assessment of ascites and hepatic encephalopathy.~~ ~~g~~ Subjects randomized to placebo during the Double-Blind Phase will receive OCA 10 mg for 3 months followed by OCA 25 mg in the OLE, unless there are safety concerns. Subjects randomized to OCA during the Double-Blind Phase will continue the treatment they were assigned. ~~h Optional procedure.~~ ~~j~~ At the Month 1, 2, 4, and 5visit, investigational product dispensed/administered will be from the bottle issued at the previous visit. ~~m Trough PK samples will be collected from all subjects at each specified Visit and must be completed prior to administration (predose) of investigational product.~~ ~~n Serial PK blood samples will be obtained 0.5 hour prior to dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post dose. All assessments, except for the post-dose collection of blood samples for subjects participating in the PK assessment, must be completed prior to~~	d **The calculations for BMI and waist-to-hip ratio will be performed via EDC: BMI from weight and height measurements, and waist-to-hip ratio from waist and hip circumference measurements. (Note: Height will be measured at Screening Visit 1 only.)** **e** Body temperature, sitting heart rate, respiratory rate, and seated blood pressure after sitting 3 minutes. **g Perform EGD procedure unless data from a recent EGD (within 6 months of OLE Day 1) are available. Subjects with varices will not continue in the OLE Phase.** **h** Subjects randomized to placebo during the Double-Blind Phase will **be re-randomize to OCA 10 mg or OCA 10 mg → 25 mg arms on OLE Day 1; the placebo subjects in the OCA 10 mg → 25 mg arm will** receive OCA 10 mg for 3 months followed by OCA 25 mg in the OLE, unless there are safety concerns. Subjects randomized to OCA **(10 mg or 25 mg dose)** during the Double-Blind Phase will continue the treatment they were assigned. **i Biopsy at Month 12 DB/Day 1 OLE, must be completed prior to receiving investigational product on Day 1 of OLE. At Month 12 of OLE and ET of OLE, the biopsy procedure is optional.** **k** At the **OLE** Month 1, 2, 4, and 5 Visit, investigational product dispensed/administered will be from the bottle issued at the previous visit.	Clarification Screening for varices (an exclusionary criterion) at the beginning of the OLE Phase. Clarification Clarification PK assessments have been removed from the OLE Phase

	~~administration of investigational product. Subjects will be permitted to decline to provide a blood sample for the genetics study without affecting their involvement in the study.~~		
Section 7.3, Planned Dosing Regimen	Subjects will be randomly assigned in a 1:1 ratio to receive placebo ~~or OCA.~~ ~~Following~~ assessments of liver chemistry and safety at Month 1 and Month ~~2, a dose titration to 25 mg or matching placebo will be implemented at Month 3~~, unless there are safety and tolerability concerns identified by the 9.2medical monitor.	Subjects will be randomly assigned in a 1:1**:1** ratio to receive **OCA 10 mg, OCA 10 mg → 25 mg, or** placebo. **For subjects in the OCA 10 mg → 25 mg group, a dose titration to 25 mg will be implemented at Month 3 after** assessments of liver chemistry and safety at Month 1 and Month **2**, unless there are safety and tolerability concerns identified by **the Medical Monitor/or the Investigator. Subjects randomized to the OCA 10 mg or placebo arms will continue the same dosing (dummy titration) (refer to Section 9.2).**	Rules for the titration arm have been clarified.
Section 7.4, Monitoring and Management of Potential Hepatic Injury and/or Disease Progression	Section 7.4, Management of Disease Progression ~~A subject who progresses to CP Class B or C cirrhosis (CP score ≥7) will discontinue investigational product (Section 8.2.1.1), and the subject should be followed for the duration of the study. 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.~~ ~~Monitoring of disease progression using CP score and MELD will be continued throughout the study (Table 1). In addition, subjects should be re-assessed within a month for disease progression. At a minimum, a physical exam, general biochemistry, serum electrolytes, and assessment of CP and MELD scores should be conducted. Further monitoring outside of regular scheduled visits should be based on the Investigator's assessment of the subject's clinical status.~~	Section 7.4, **Monitoring and** Management of **Potential Hepatic Injury and/or** Disease Progression **To monitor for potential hepatic injury, disease progression and/or hepatic decompensation, Child-Pugh and MELD scores will be reviewed at each visit (Section 7.1.2). In addition, adverse events, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will also be reviewed at regular intervals as described in the following subsections (Section 7.4.1 to Section 7.4.3). Based on the assessments of signs and symptoms of hepatic injury and liver biochemistry, the investigational product will be interrupted or discontinued per criteria discussed in Section7.5, and close monitoring procedures will be implemented (refer to Section 7.6).**	Additional safety procedure added to the protocol.

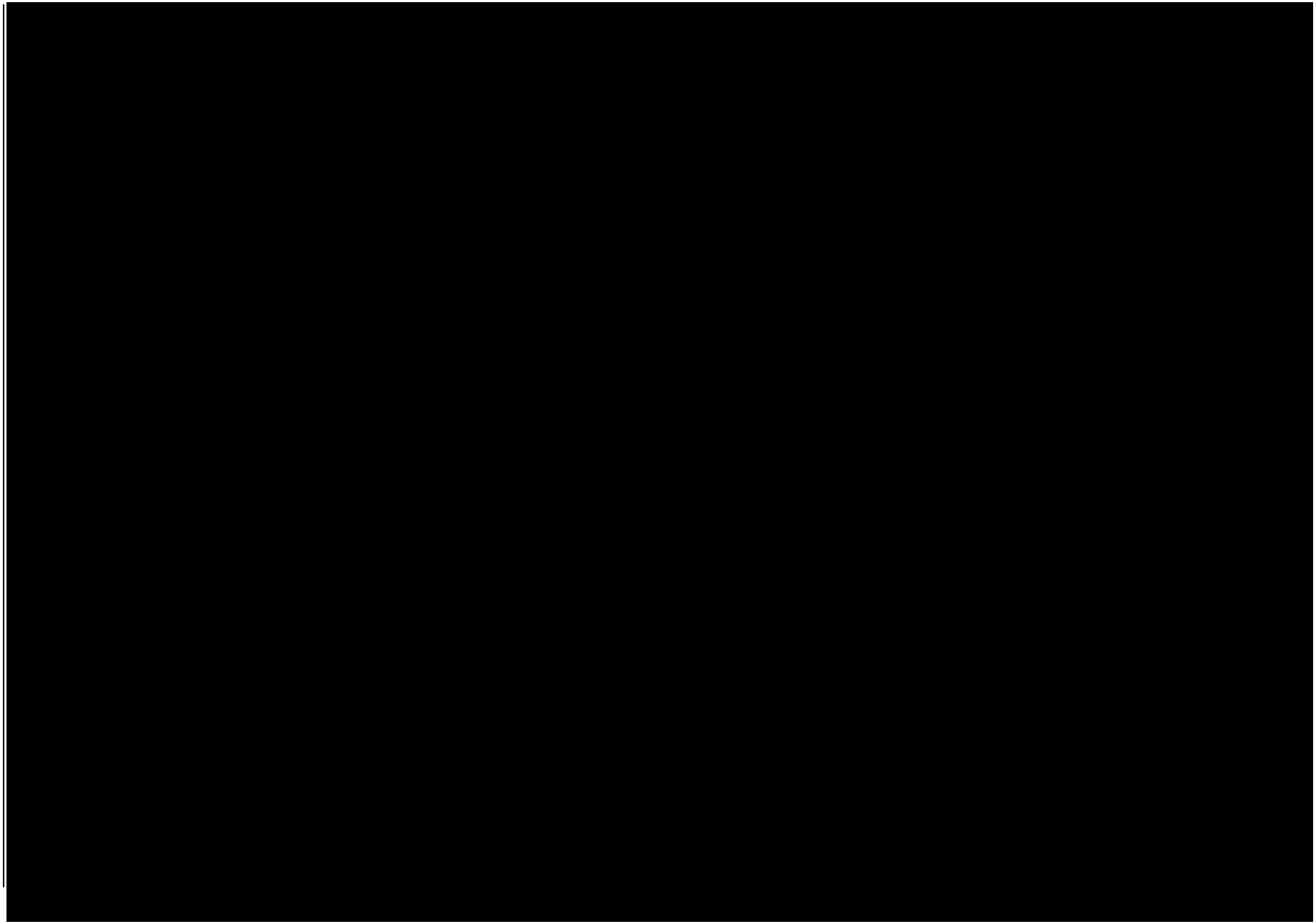
Section 7.4.1, Signs and Symptoms of Hepatic Injury or Decompensation		**Subjects will be evaluated at study visits for potential signs and symptoms of hepatic injury or decompensation:** **Signs and Symptoms of Hepatic Injury or Decompensation:** **• Specific signs and symptoms of liver impairment: 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: confusion, swelling of the legs or abdomen** **• Non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite** **• Significant intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and diarrhea for more than 4 days) and should be an indication for prompt investigational product interruption and complete subject evaluation** **Other Symptoms:** **• New or worsening pruritus** **• Worsening of renal function or likely dehydration** **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**	Additional safety procedure added to the protocol.

		Signs and symptoms for potential hepatic injury or decompensation should be followed by (1) evaluation of liver biochemistry for drug-induced liver injury (DILI) (Section 7.4.2), (2) assessment for disease progression (Section 7.4.3), (3) triggering of investigational product interruption or discontinuation per criteria (Section 7.5), (4) documentation in the AE eCRF or the SAE eCRFs (Section 15.1.4 and Section 15.1.5), and (5) contact with the Medical Monitor.	

Section 7.4.2, Drug-Induced Liver Injury		**Liver biochemistry will be assessed at each visit to assess biochemical triggers that will prompt an immediate reevaluation of subjects. Thus, these assessments will be performed at:** **• Each protocol-specified visit** **• Unscheduled visits for any safety follow-up as appropriate** **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 mandatory repeat testing and potentially a complete subject evaluation (depending on the repeat result) are summarized in Table 3.** **(Figure 2)** **(Table 3)** **If any subject meets the triggering threshold limits for either conjugated bilirubin or creatinine, investigational product should be immediately interrupted (see Section 7.5 for dosing modifications).** **For the remaining liver biochemistry assessments, if a subject meets the upper threshold limits, the laboratory assessment should be repeated in 2 to 3 days (with the**	Additional safety procedure added to the protocol.

		exception of ALP, which should be repeated in 7 days). If a repeat laboratory test cannot be performed within 2 to 3 days, the subject should be instructed to interrupt investigational product until repeat lab results have been reviewed. **• If on repeat evaluation, values are normal or returned or trended back to prior values, no dosing modifications are required and the subject should continue to be monitored.** **• If on repeat evaluation, values remain above the specified threshold, investigational product should be interrupted (see Section 7.5 for dosing modifications). In this case, a medical history and physical exam should be conducted and AE information (including signs and symptoms of liver injury as described in Section 7.4.1) collected. The medical monitor should be promptly contacted upon awareness for consultation regarding management of the subject. If symptoms persist or repeat testing shows persistent abnormality as described above, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening.** **Subjects should, wherever possible, come back to the site. It may be difficult for subjects who are distant from their study site to return to the site promptly. Such subjects can have repeat (or any safety) laboratory tests performed at a local laboratory, but normal laboratory ranges and the results should be made available to the Investigator, and redacted copies provided to the Sponsor.** **It should be noted that it is difficult to recognize every potential marker of hepatic or renal deterioration. 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 artefactual; 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.	
Section 7.4.2, Drug-Induced Liver Injury, Figure 2, DILI Management Algorithm for Study 747-304		[redacted]	Additional safety procedure added to the protocol.



		Electrolytes[c] | Sodium <130 | 2-3 days **NA = not applicable** **a Diagnosis of Gilbert's Syndrome should be established during baseline. Conjugated bilirubin to be sole determinate in such subjects.** **b Does not apply in subjects on anti-coagulants** **c Sodium will be measured as an assessment of liver failure (hyponatremia).**	
Section 7.4.3, Progression of Disease to Child-Pugh Class B or C		**Investigators will closely monitor subjects for potential progression of cirrhosis to CP Class B or C at every visit (or at unscheduled visits in the event of signs or symptoms of suspected hepatic injury or decompensation). Assessment of CP Scores must be performed at every visit. Refer to Section 7.4.3.1 for determination of CP Score. Investigational product discontinuation is required in subjects who progress to CP score of 7 or higher.**	Additional safety procedure added to the protocol.

<table>
<tr>
<td>Section 7.4.3.1, Child-Pugh Assessment</td>
<td></td>
<td>
Child-Pugh (CP) Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 4 and can range from 5-15. The investigational product should be discontinued in subjects with CP score ≥7.
Calculation of the CP Score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory. The relationship of CP Score to disease progression is as follows: CP score 5-6 = CP Class A; CP Score 7-9 = CP Class B; CP Score ≥10 = CP Class C.
Table 4: Child-Pugh Scoring System
<table>
<tr><th rowspan="2">Factor</th><th rowspan="2">Units</th><th colspan="3">Points</th></tr>
<tr><th>1</th><th>2</th><th>3</th></tr>
<tr><td rowspan="2">Serum bilirubin</td><td>µmol/L</td><td><35</td><td>35-50</td><td>>50</td></tr>
<tr><td>mg/dL</td><td><2.0</td><td>2.0-3.0</td><td>>3.0</td></tr>
<tr><td rowspan="2">Serum albumin</td><td>g/L</td><td>>35</td><td>28-35</td><td><28</td></tr>
<tr><td>g/dL</td><td>>3.5</td><td>2.8-3.5</td><td><2.8</td></tr>
<tr><td rowspan="2">Prothrombin time</td><td>Seconds prolonged</td><td>0-3</td><td>4-6</td><td>>6</td></tr>
<tr><td>INR</td><td><1.7</td><td>1.7-2.3</td><td>>2.3</td></tr>
<tr><td>Ascites</td><td></td><td>None</td><td>Mild</td><td>Moderate-Severe</td></tr>
<tr><td>Hepatic encephalopathy[a]</td><td></td><td>No</td><td>Grade 1 or 2</td><td>Grade 3 or 4</td></tr>
</table>
INR = international normalized ratio
Child-Pugh criteria: Pugh 1973, Lucey 1997.
West Haven criteria: Vilstrup 2014.
a Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
</td>
<td>Additional safety procedure added to the protocol.</td>
</tr>
</table>

		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**	
Section 7.4.3.2, Model for End-Stage Liver Disease (MELD) Scoring		**MELD is a scoring system used to assess the severity of chronic liver disease. An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk. MELD scores will be calculated based on creatinine, bilirubin, INR, and sodium values as appropriate, collected at the same visit with modification by United Network for Organ Sharing. If only 1 component of MELD needs to be repeated, all other components should also be repeated. INR will be calculated based on PT value by the central laboratory. The MELD calculation adjusts for subject who have had 2 or more dialysis treatments within the prior week and will automatically assign a serum creatinine of 4.0 mg/dL for these subjects.**	Additional safety procedure added to the protocol.

Section 7.4.4, Pruritus		**Pruritus is already being closely monitored but has not been shown to be a reliable predictor of hepatic injury. However, Investigators should be vigilant in responding to subjects' complaints of new or worsening pruritus symptoms with prompt follow-up. Pruritus grading (as with all adverse events) should be performed in accordance with CTCAE Version 4.03 (Appendix B).** **For subjects with Grade 3 pruritus per CTCAE Version 4.03 (Section 15.1.4.1), instruct the subject to discontinue investigational product (Table 5). These subjects should continue to return for scheduled study visits for safety follow up; however, the subjects will not be rechallenged with investigational product. General guidance for the management of subjects experiencing significant pruritus (≤Grade 2) is provided in Table 5 and Section 14.1.4.1.**	Safety procedures

<table>
<tr>
<td>Section 7.5. Investigational Product Dosage Interruption and Discontinuation Criteria</td>
<td>7.5. Dosage <s>Adjustment</s> Criteria

<s>With an exception of the planned dose titration at Month 3,</s> dosages for investigational product should be maintained constant during the study. However, <s>dose frequency may be modified for the management of pruritus or other safety findings as</s> described in Section <s>15.1.4.1</s>.
<s>In the event of tolerability issues such as pruritus, the dosing frequency may be decreased at the discretion of the Investigator.</s>
<s>If at any point, safety concerns are noted based on review of liver biochemistry and adverse events, down titration to 10 mg daily may be considered in consultation with the medical monitor.</s>
Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns.
Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study.
<s>Refer to Section 8.2.1 for guidance on mandatory discontinuation of investigational product due to severe and related AEs, severe drug-induced liver injury, liver transplantation, and bariatric surgery.</s>
<s>Refer to Section 8.2.2 for guidance on mandatory interruption of investigational product due to AEs ≥ Grade 4 or drug-induced liver injury discontinuation of investigational product.</s>
<s>8.2.2Refer to Section 8.2.3 for other reasons discontinuation of investigational product (eg, withdrawal of consent, lost to follow-up, or pregnancy).</s></td>
<td>7.5. Investigational Product Dosage Interruption and Discontinuation Criteria
Dosages for investigational product should be maintained constant during the study. However, interruptions, discontinuation, and any rechallenge of investigational product should be implemented per the criteria outlined in Table 5. Planned uptitration at Month 3 in the OCA 10 mg → 25 mg arm (Double-Blind Phase) and in placebo subjects at OLE Month 3 is described in Section 9.2.
Subjects can be temporarily or permanently discontinued from investigational product by the Investigator at any time for clinical safety concerns.
• Subjects who are temporarily discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study.
• Subjects who permanently discontinue from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. These subjects will not be rechallenged with investigational product.
Prior to re-starting investigational product after a prolonged interruption, the subject must be re consented and new baseline visit procedures must be performed (refer to Section 8.2.2) if the interval from the last visit was more than 1 month (+2 weeks).

Table 5: Criteria for Dose Interruption, Discontinuation, and Rechallenge
<table>
<tr><th>DOSE INTERRUPTION</th><th></th><th></th></tr>
<tr><td>Criteria</td><td>Action Taken with IP[a]</td><td>Rechallenge[b,c]</td></tr>
</table>
</td>
<td>Additional safety procedure added to the protocol.</td>
</tr>
</table>

		If either of the 2 following liver biochemistries exceeds upper threshold criteria: • **Conjugated bilirubin** • **Creatinine**	**Interrupt immediately upon initial observation**	**Subject may be rechallenged after a minimum of 30 days if fully resolved and stable and approved by the Medical Monitor and Investigator.**		
		Other liver lab values[d] are outside upper threshold criteria	**Interrupt after confirmation by repeat testing**			
		Gastroenteritis (established severe abdominal pain, vomiting, diarrhea for more than 4 days)	**Interrupt**	**If no evidence of liver injury is detected, IP may be restarted at a reduced dosing frequency after resolution or stabilization of intercurrent illness.**		
		Evidence of worsening of renal function or dehydration	**Interrupt**			
		AE categorized as ≥Grade 4 in severity and not or unlikely related to IP	**Interrupt**			
		Pregnancy	**Interrupt**	**Subject should continue with the study visit schedule. The subject may re-start investigational product when she is no longer pregnant or breastfeeding (if applicable) at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 15.1.11.**		
		DOSE DISCONTINUATION				
		Criteria	**Action Taken with IP**	**Rechallenge**		
		Potential Hepatic Decompensation[e] or Progression to Child Pugh B or C [CP Score ≥7]	**Discontinue[f] / No Rechallenge**	**Continue to return for scheduled study visits for safety follow up; however, the subject should**		

			not be rechallenged. Monitor closely for clinical outcomes according to protocol assessments.	
≥Grade 3 pruritus[g] Other AEs ≥Grade 3 considered possibly, probably, or definitely related to IP Liver transplantation Bariatric Surgery		Discontinue[f] / No Rechallenge	Continue to return for scheduled study visits for safety follow up; however, the subject should not be rechallenged.	

Fully resolved = Return to baseline levels or return to within normal limits (WNL). IP = investigational product

a If subject is unable to be evaluated promptly, investigational product must be immediately interrupted.

b Requires complete documentation of complete resolution or normal/baseline based on laboratory parameters and symptoms.

c The Investigator may rechallange at the same dose or reduced dosing frequency of the investigational product.

d ALT, AST, ALP, total bilirubin, INR, GGT, albumin, platelets, and electrolytes (sodium).

e Clinically evident complications of portal hypertension (eg, ascites, variceal hemorrhage, hepatic encephalopathy).

f Subjects who permanently discontinue from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study.

g Severity per CTCAE Version 4.03.

Section 7.6, Close Observation		**If investigational product is interrupted or discontinued as described in Section 7.5, subjects should be closely monitored. If returning to the site for a scheduled visit is not feasible, use of a local lab may be permissible at the Investigator's discretion. Subjects who permanently discontinue from investigational product should continue regularly scheduled visits.** **At a minimum, the following assessments should be conducted at each study visit:** **• Physical exam and thorough review of subject reported signs and symptoms,** **• Liver biochemistry (including ALP, ALT, AST, GGT, total and conjugated bilirubin, creatinine, and albumin), prothrombin time (PT)/INR, serum electrolytes, and assessment of Child Pugh (only if the subject is at the study site) and MELD scores.** **In addition, a pharmacokinetic sample for assessment of OCA serum drug levels and its major metabolites should be obtained in any subject who develops an AE of hepatic injury or decompensation.** **For events of potential hepatic injury, the following additional monitoring procedures should be performed per FDA Guidance for Industry on Drug Induced Liver Injury. These cases must to be discussed with the Sponsor's medical monitor:** **• Repeating liver enzyme and serum bilirubin tests as described in Table 3. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic, as clinically indicated.** **• Obtaining a more detailed history of symptoms and prior or concurrent diseases.**	Additional Safety Procedures

		• Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs potentially hepatotoxic, continued use of investigational product should be discussed with the Sponsor's medical monitor. The subject may be discontinued from investigational product, if clinically appropriate. **• Obtaining a history of exposure to environmental chemical agents or herbal supplements which may be associated with liver toxicity.** **• Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute HBV infection), and E; autoimmune or alcoholic hepatitis; Wilson disease, hypoxic/ischemic hepatopathy; and biliary tract disease.** **• Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).** **• Seeking hepatology consultation, if the Investigator is not a hepatologist.**	

Section 8.2, Subject Withdrawal Criteria (Section 8.2 to Section 8.2.1.3)	*Section 8.2 and its subsections were rearranged and updated in Version 3. The headers in Version 2 were as follows:* 8.2. Subject Withdrawal Criteria 8.2.1. Reasons for ~~Mandatory~~ Discontinuation of Investigational Product 8.2.1.1. ~~Progression to CP score ≥7~~ 8.2.1.2. ~~Severe and Related Adverse Events~~ 8.2.1.3. ~~Liver Transplantation~~ ~~8.2.1.4 Bariatric Surgery~~ ~~8.2.2 Reasons for Mandatory Interruption of Investigational Product~~ ~~8.2.2.1. Adverse Events ≥ Grade 4 in Severity and Not or Unlikely Related to Investigational Product~~ ~~8.2.2.2. Suspected Drug-Induced Liver Injury~~ ~~8.2.3. Other Reasons for Discontinuation of Investigational Product or Study Termination~~ ~~8.2.3.1.~~ Withdrawal of Consent to Continue in the Study ~~8.2.3.2.~~ Lost to Follow-Up ~~8.2.3.3.~~ Pregnancy	*Section 8.2 and its subsections were rearranged and updated in Version 3. The headers in Version 3 are as follows:* 8.2. Subject Withdrawal Criteria 8.2.1. Other Reasons for Discontinuation of Investigational Product or Study Termination **8.2.1.1.** Withdrawal of Consent to Continue in the Study **8.2.1.2**. Lost to Follow-Up **8.2.1.3.** Pregnancy	Clarifications
The specific changes in text are as follows:	***The specific changes in text are as follows:*** 8.2. Subject Withdrawal Criteria ~~8.2.1. Reasons for Mandatory Discontinuation of Investigational Product~~ ~~8.2.1.1. Progression to CP score ≥7~~ ~~If a subject develops a CP score ≥7, liver related assessments used in CP score calculation should be confirmed within 48 to 72 hours and captured in the EDC. If CP score is confirmed, a mandatory discontinuation of investigational product is required. However, subjects should be~~	***The specific changes in text are as follows:*** 8.2. Subject Withdrawal 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 are expected to continue in the study and should follow the regular visit schedule for the duration of the study phase (Double Blind or OLE). Subjects who permanently discontinue from investigational product are expected to continue regular visit schedule for safety**	

	~~encouraged to continue study visits, despite stopping investigational product, for continued collection of safety data but may withdraw consent at any time.~~ ~~8.2.1.2. Severe and Related Adverse Events~~ ~~If a subject experiences an AE that is ≥Grade 3 in severity using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) (Section 15.1.4) and is considered possibly, probably, or definitely related to 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.~~ ~~8.2.1.3. Liver Transplantation~~ ~~Subjects must discontinue investigational product after undergoing liver transplantation surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection but may withdraw consent at any time.~~ ~~8.2.1.4. Bariatric Surgery~~ ~~Subjects must discontinue investigational product after undergoing bariatric surgery. A biopsy should be obtained at the time of surgery. Subjects should be encouraged to continue study visits, despite stopping investigational product, for continued study data collection but may withdraw consent at any time.~~ ~~8.2.2. Reasons for Mandatory Interruption of Investigational Product~~ ~~8.2.2.1. Adverse Events ≥ Grade 4 in Severity and Not or Unlikely Related to Investigational Product~~ ~~If a subject experiences an AE categorized as ≥ Grade 4 in severity and not or unlikely related to~~	**assessments until stabilization of the clinical event has occurred leading to discontinuation (per discretion of the Investigator and upon discussion with the medical monitor).** **Refer to Section 7.4 and Section 7.5 for withdrawal criteria related to potential hepatic injury and/or decompensation; progression to cirrhosis with CP score ≥7; Grade 3 pruritus, AEs ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product; AEs ≥Grade 4 in severity and NOT or unlikely related to investigational product; liver transplantation, bariatric surgery, and pregnancy. Other reasons, including withdrawal of consent or lost to follow up, are described in Section 8.2.1 below.**	

	~~investigational product, at least a mandatory interruption of investigational product is required.~~ ~~8.2.2.2. Suspected Drug-Induced Liver Injury~~ ~~Cirrhotic patients have diminished liver reserve and lesser ability to recover, and these could make the consequences of a drug induced injury worse. Their transaminase, especially ALT, levels may be normal or only slightly elevated, due to their lower hepatocellular reserve, even in advanced cases. For this reason, relatively lower level of transaminase elevations can indicate severe drug induced liver injury and may require investigational product discontinuations.~~ ~~Subjects who discontinue investigational product are expected to be followed though to study closure (or at the discretion of the Sponsor) and should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time.~~ ~~Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued. Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.~~ ~~Investigational product must be interrupted in subjects if the following conditions develop:~~ ~~• Baseline values were <2x ULN, and ALT or AST increases to >5x baseline measurement (BLM).~~ ~~• Baseline values were ≥2x ULN but <5x ULN, and ALT or AST increases to >3x BLM.~~ ~~• Baseline values were ≥5x ULN, and ALT or AST increases to >2x BLM.~~		

	~~• ALT or AST increase >2x BLM AND the increase is accompanied by a concomitant total bilirubin increase to >2x BLM OR the INR concomitantly increases by >0.2.~~ ~~Investigational product will also be interrupted in presence of signs and symptom(s) such as rash, eosinophilia, nausea, vomiting, or right upper quadrant pain, anorexia and fatigue irrespective of the transaminase level, if the bilirubin is elevated above 2x BLM. A potential drug-induced liver injury work-up for competing etiologies must be performed, and a complete liver profile including prothrombin time (PT)/INR must be repeated within 48-72 hours. Study medication can be restarted only if an alternative etiology is definitively identified and liver tests have returned to baseline.~~ ~~Follow-up procedures, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. In this case, results as well as normal laboratory ranges, must be reported immediately to the site, and included in the case reports, so the Investigator can determine if the subject is to be allowed to continue treatment.~~ ~~8.2.3.~~ Other Reasons for Discontinuation of Investigational Product or Study Termination - Consent may be modified to discontinue study visits but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE), and liver-related clinical outcomes~~, and drug-related hepatic injury events~~	**8.2.1.** Other Reasons for Discontinuation of Investigational Product or Study Termination - Consent may be modified to discontinue study visits but allow continued access to medical records to assess for suspected major adverse cardiovascular events (MACE), **and** liver-related clinical outcomes	

Section 8.2.2, Reinitiating Investigational Product After Interruption	Prior to restarting investigational product after a prolonged interruption (ie, longer than ~~4 weeks~~), the subject must be reconsented. New baseline procedures must be performed if the interval from the last visit was more than ~~3~~ months during the study. ~~• Samples for genetic analyses (optional)~~ • Noninvasive radiological liver fibrosis measurement~~s~~ (transient elastography [TE]~~,~~ ~~LiverMultiScan, and magnetic resonance elastography [MRE~~]; conducted at sites where device is available). ~~Whichever modality/ies used at baseline must be collected consistently at each visit.~~	Prior to restarting investigational product after a prolonged interruption (ie, longer than **1 month [+2 weeks]),** the subject must be reconsented. New baseline procedures must be performed if the interval from the last visit was more than **1** month **(+2 weeks)** during the study. • **Perform hepatobiliary ultrasound for HCC screening unless data from a recent ultrasound (within 3 months) are available** • Noninvasive radiological liver fibrosis measurement (transient elastography [TE]; conducted at sites where device is available).	
Section 7.5, Dosage Adjustment Criteria		**If during the study, a subject progresses to CP score ≥7 (CP Class B or C), the Investigator should discontinue investigational product. In addition, subjects should be re-assessed monthly (or more frequently per Investigator discretion) for at least 3 months or until clinically stable.**	Additional safety procedure added to the protocol.
Section 8.2, Subject Withdrawal Criteria		*The following text was moved from Section 7.4 of protocol version 2 to Section 8.2 of protocol version 3.* Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study **phase (Double-Blind or OLE).**	Clarification

Section 9.1, Investigational Product Treatment Regimen	~~Two~~ treatment groups will be evaluated: • Placebo • OCA (10 mg ~~and 25 mg~~) ~~9.1.1. OLE Phase~~	**Three** treatment groups will be evaluated: • Placebo • OCA (10 mg) • **OCA (10 mg → 25 mg)** **The study will be blinded until the last subject completes the Double-Blind Phase and the database is locked.**	Clarifications

Section 9.2, Uptitration at Month 3. Section 9.2.1, Double-Blind Phase	*Section 9.2, 9.2.1, and 9.2.2 were added to Version 3*	**9.2. Uptitration at Month 3** **9.2.1. Double-Blind Phase** **Subjects randomized to the OCA 10 mg → 25 mg arm in the Double-Blind Phase will receive OCA 10 mg for the first 3 months. Uptitration to 25 mg may occur at Month 3, following review of individual subject safety and tolerability data.** **Prior to the Month 3 study visit, the Medical Monitor will perform a review of consolidated safety data, including data from the Month 1 and 2 study visits, as well as that from any unscheduled visit(s), for all study subjects. Case review and discussion with the principal investigator will occur as needed. A subject may proceed with uptitration to OCA 25 mg (or matching placebo), if no safety and/or tolerability concerns are evident in the clinical judgement of the reviewer(s). The review will include but not be limited to the following:** **• Liver-related adverse events** **• Safety laboratories: chemistry panel including glucose, hematology panel, coagulation parameters; computed MELD score and Child-Pugh score** **• Physical examination (development of clinically evident ascites or manifestations of hepatic encephalopathy)** **Additional considerations to determine the suitability to uptitrate will include an assessment of comorbid conditions, the subject's overall adverse event profile, concomitant medications with a focus on potentially hepatotoxic concomitant medications, and/or any new treatment(s) for comorbid condition(s). The uptitration review process is detailed in the study-specific Medical Management Plan.**	Clarification of dosing instructions for the titration arm

Section 9.2.2, OLE Phase		**If uptitration at Month 3 is not feasible due to special circumstances, the window for uptitration may be extended by up to one calendar month, after consultation and agreement with the Medical Monitor.** **Subjects randomized to the OCA 10 mg or placebo arms will undergo dummy titration to maintain study blind.** **In addition, dosing frequency post-titration may be temporarily decreased for tolerability reasons, following discussions with the Medical Monitor. In addition, investigational product may be interrupted per safety criteria listed in Table 5 and Section 7.5. The procedures for re initiating investigational product after prolonged interruption are provided in Section 8.2.2** **9.2.2. OLE Phase** **Subjects who were randomized to placebo in the Double-Blind Phase will be re-randomized to either OCA 10 mg or OCA 10 mg → 25 mg at entry into the OLE. Uptitration to OCA 25 mg at Month 3 in the OLE will be conducted in the same manner applied in the Double-Blind Phase and described above. Subjects randomized to OCA (10 mg or 25 mg dose) during the Double-Blind Phase will continue the same dosing regimen.** **All dosing will be conducted in a dummy titration fashion in order to maintain the blind until all subjects complete the Double-Blind Phase and the database is locked.**	

Section 9.2, Concomitant Medications	Relevant information about all concomitant medications taken before (ie, within ~~6~~ months of Day 1) and during the study must be recorded in the source documents and case report form, as well as any dose or dose regimen changes that occur during the study. To the extent possible, concomitant medications should be maintained at a stable dose throughout the study and at a minimum, from Day 1 through the end of double-blind ~~treatment~~, unless the baseline therapy is no longer considered clinically appropriate by the Investigator or the subject's primary care provider.	Relevant information about all concomitant medications taken before (ie, within **12** months of Day 1) and during the study must be recorded in the source documents and case report form, as well as any dose or dose regimen changes that occur during the study. To the extent possible, concomitant medications should be maintained at a stable dose throughout the study and at a minimum, from Day 1 through the end of **the** Double-Blind **Phase**, unless the baseline therapy is no longer considered clinically appropriate by the Investigator **or the subject's primary care provider**. **The restrictions related to use of drugs historically associated with drug induced NAFLD are as follows:** **• Drugs with Potential NASH-modifying Properties** **Subjects should either not be taking any drugs with potential NASH-modifying properties (specifically, TZDs/glitazones or vitamin E) or be on a stable dose of these medications for 6 months before Day 1. Subjects providing historical biopsies to determine study eligibility should be on a stable dose of these medications for 12 months before Day 1 and these medications should not have been initiated after the historical liver biopsy was performed. Changes to these drugs with potential NASH-modifying properties are not permitted for the duration of the Double-blind Phase unless the baseline therapy is no longer considered clinically appropriate by the Investigator/or the usual care provider.** **• Drugs with Potential NAFLD-inducing Properties** **Subjects chronically (≥12 months) using the following drugs, that are historically associated with NAFLD, will not be enrolled in the study:**	Restrictions related to use of drugs with potential NASH-modifying properties and drugs historically associated with drug induced NAFLD are clarified in this section.

		amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid, and other known hepatotoxins (refer to exclusion criterion 28; Section 8.1.2).	
Section 9.3.1, Statins	Use of statins (eg, simvastatin, atorvastatin) should be at a stable dose ~~1 month~~ before Day 1.	Use of statins (eg, simvastatin, atorvastatin) should be at a stable dose **≥30 days** before Day 1.	Clarification
Section 9.5.1, Methods of Assigning Subjects to Treatment Groups	9.4.1. Methods of Assigning Subjects to Treatment Groups This study will be conducted in a double-blind, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1 ratio to placebo ~~or OCA~~ based on a predefined randomization code (generated by Sponsor or designee~~) using an IWRS~~. Subjects randomized to OCA will initiate ~~investigational product of~~ OCA 10 mg for 3 months prior to uptitrating to OCA 25 mg. Uptitration will be based on safety and tolerability assessments completed ~~at Month 1~~, Month9.2 2, and Month 3. Randomization of subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no~~) and cryptogenic cirrhosis (yes or no).~~ All subjects who enroll into the OLE will receive OCA. 9.2Subjects randomized to placebo in the double-blind period will initiate investigational product of OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg. Uptitration will be based on safety and tolerability assessments completed at Month 1, Month 2, and Month 3. Subjects will continue the same dosing regimen they received at the end of the Double-Blind Phase. ~~Once all subjects have titrated to the 25 mg dose in the OLE, subjects may receive investigational product with an open label identifying the product as OCA 25 mg.~~	9**.5**.1. Methods of Assigning Subjects to Treatment Groups This study will be conducted in a double-blind, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1**:1** ratio to **one of the three treatment arms: once daily dosing of OCA 10 mg, OCA 10 mg → 25 mg (ie, OCA 10 mg with uptitration to OCA 25 mg at Month 3), or** placebo. **Randomization will be done using an IWRS and will be** based on a predefined randomization code generated by **the** Sponsor or designee. Subjects randomized to OCA **10 mg → 25 mg** will initiate **dosing at** OCA 10 mg for 3 months prior to uptitrating to OCA 25 mg. Uptitration will be based on safety and tolerability assessments completed **prior to** Month **3 (Section 9.2)**. Randomization of subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no). All subjects who enroll into the OLE will receive OCA**. Subjects randomized to placebo in the Double-Blind Phase will be re-randomized to OCA 10 mg or OCA 10 mg → 25 mg arms, with uptitration at OLE Month 3 in the OCA 10 mg → 25 mg arm (refer to Section 9.2).**	Clarification

Section 9.5.2, Blinding	9.~~4~~.2. Blinding The subjects, Investigators, and study site staff will be blinded to the subject's treatment ~~allocation during the subject's participation in the study~~.	9.**5**.2. Blinding The subjects, Investigators, and study site staff will be blinded to the subject's treatment **regimen until all subject data have been collected from the study and the database is locked. Using this approach, blinding of the trial will be maintained**.	Clarification
Section 9.6.2, Subject Numbers	9.~~5~~.2. Subject Numbers Subjects ~~will be identified by~~ a unique ~~6~~-digit number. The first 3 digits ~~will~~ represent the site number ~~and the~~ last 3 digits, ~~the subject~~ number.	9.**6.**2. Subject Numbers Subjects **are assigned using** a unique **10-character, 9**-digit **identifier (AAA BBBCCC), independent of the randomization** number. The first 3 digits **represent the last 3 digits of the protocol number, followed by a hyphen (AAA-). The next 3 digits** represent the site **number (BBB). The** last 3 digits **represent a unique screening** number **that is assigned in sequential order at each site starting with 001 (CCC).**	Clarification
Section 9.8, Visit Procedures	9.~~7~~. Visit Procedures Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. ~~For example~~, Month 3 should ideally occur ~~3 calendar months~~ (±1 week~~) following Day 1. A~~ month ~~is defined as 4 weeks (ie, 28 days)~~. Acceptable windows for PK sampling timepoints are in Table ~~5.~~	9.**8**. Visit Procedures Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. **If Day 1 occurs on January 1st**, Month 3 should ideally occur **on April 1st** (±1 week**). This is the definition of a calendar** month. Acceptable windows for PK sampling timepoints are in Table **7**.	Clarification
Section 9.8.1,	Subjects will also be required to provide consent prior to participating in any of the optional assessments, such as providing blood samples for ~~genetic analysis or~~ serial PK draws	Subjects will also be required to provide consent prior to participating in any of the optional assessments, such as providing blood samples for serial PK draws.	Genetic analysis assessments have been removed from the study.

Section 9.8.2, Fasting Requirement at Study Visits	9.~~7.~~2. Fasting Requirement at Study Visits Starting ~~on Day 1~~, all subjects must arrive to the study site in a fasted state (at least 8 hours before each visit).	9.**8**.2. Fasting Requirement at Study Visits Starting **with Screening Visit 2**, all subjects must arrive to the study site in a fasted state (at least 8 hours before each visit). **If the subject reports having eaten within 8 hours of the visit, the nonfasted state will be documented in the source and eCRF; however, scheduled assessments (blood collection) will still be performed during the visit, and these subjects will be reminded that fasting is required before all study visits.**	Correction made – fasting is also required at Screening Visit 2

Section 9.8.3.1, Screening Visit 1 *through* Section 9.8.10, DB Month 12/EOT/EOS	*Changes across multiple sections from Section 9.~~7~~.3.1 through 9.~~7.11~~ are indicated below by visit days:* SV1, SV2, D1 • Assess and record any pretreatment-~~emergent~~ AEs (after the ICF has been signed) SV1, SV2 • Record prior (if within ~~6~~-months of Day 1) and current concomitant medications SV1, D1, M6, M12 • Perform hepatobiliary ultrasound for HCC screening unless data from a recent historic ultrasound (within 3 months of ~~Screening~~) are available SV1, M1, M2, M3, M4, M5, M9 ~~• Lipoprotein analysis~~ SV1, SV2, M1, M6, M12, and ET • Noninvasive radiological liver fibrosis measurements (TE~~, LiverMultiScan, and MRE~~; conducted at sites where device is available)	*Changes across multiple sections from Section 9.**8**.31 through 9.**8.10** are indicated below by visit days:* SV1, SV2, D1 • Assess and record any pretreatment AEs (after the ICF has been signed) SV1, SV2 • Record prior (if within **12** months of Day 1) and current concomitant medications SV2 through M12, and ET • Measure circumference of waist and hips SV1, D1, M6, M12 • Perform hepatobiliary ultrasound for HCC screening **and gallbladder assessment** unless data from a recent historic ultrasound (within 3 months of **Day 1**) are available (M1) • If a hepatobiliary ultrasound for HCC screening **and gallbladder assessment** was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound (M6, M12) Perform hepatobiliary ultrasound for HCC screening **and gallbladder assessment** SV1, SV2, M1, M6, M12, and ET • Noninvasive radiological liver fibrosis measurements (TE; conducted at sites where device is available)	Editorial Clarification Gathering additional data at Screening may be beneficial in identifying at risk populations (eg, to assist with the causality of potential gallbladder/pancreatic complications. LiverMultiScan assessment has been removed from the

	~~Whichever modality/ies used at baseline must be collected consistently at each visit.~~ SV1 through M12, and ET - CP Score/Class D1, M1, M3, M6, M12, and ET ~~• Obtain stool sample (collected at home) for microbiome/metabolome analysis (US subjects only)~~ D1, M12, and ET ~~- Genetic analyses (optional)~~ M1, M4, and M12 • If subject consented to participate in serial PK assessment, the following procedures will be conducted ~~- 0.5 hour to dosing: collect predose blood sample~~	SV1 through M12, and ET - CP Score/Class **(assessment of ascites and hepatic encephalopathy is required)** M1 through M12, and ET **• Assess signs and symptoms of hepatic injury or decompensation** **- DILI management algorithm (liver biochemistry)** M1, M4, and M12 • If subject consented to participate in serial PK assessment, the following procedures will be conducted	study due to feasibility issues Clarification Additional safety procedures Microbiome/metabolome analyses have been removed from the study Clarification

Section 9.8.3.1, Screening Visit 1	9.~~7~~.3.1. Screening Visit 1 The Screening Visit assessments must be performed within ≤~~8~~ weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. ~~For~~ rescreening, all Screening procedures should be repeated and a new ~~3-digit~~ screening number assigned. Subjects should be reconsented, as appropriate, at this time. • Record weight and BMI • Determine alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT] questionnaire) For subjects without a recent liver biopsy with unstained slides, ~~a second Screening Visit (Screening Visit 2, [Section 9.7.3.2])~~ must be performed within the ~~8~~-week screening window before Day 1 (assuming all other Screening assessments indicate a likelihood that the subject will qualify based on biopsy). Note: Noninvasive radiological measurements may be completed any time ~~after~~ Screening Visit 1 through Day 1 but should be conducted prior to an on- study liver biopsy. ~~• Thyroid hormones~~	9.**8**.3.1. Screening Visit 1 The Screening Visit assessments must be performed within ≤**12** weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. **When** rescreening, all Screening procedures should be repeated and a new screening number assigned. Subjects should be reconsented, as appropriate, at this time. • **Measure height**. Record weight and BMI • Determine alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT] questionnaire)**, smoking habits, and caffeine consumption** • **Perform EGD procedure unless data from a recent EGD (within 6 months of Day 1) are available. Subjects with varices will not be enrolled in the study.** For subjects without a recent liver biopsy with unstained slides, **or adequate tissue block, an on-study liver biopsy** must be performed within the **12**-week screening window before Day 1 (assuming all other Screening assessments indicate a likelihood that the subject will qualify based on biopsy). Note: Noninvasive radiological measurements may be completed any time **during** Screening Visit 1 through Day 1 but should be conducted prior to an on- study liver biopsy**, if one is necessary, and before initiation of investigational product on Day 1**.	Screening period has been extended. Clarifications Subjects will be screened for the presence of varices at Screening Clarification Clarification

Section 9.8.3.2, Screening Visit 2	9.~~7~~.3.2. Screening Visit 2 Screening Visit 2 procedures must be performed ~~within ≤~~4 weeks ~~±2 days prior to Day~~ 1 and are as follows:	9.**8**.3.2. Screening Visit 2 Screening Visit 2 procedures must be performed ≥4 weeks **after Screening Visit** 1 and are as follows: **• For subjects without a recent liver biopsy with unstained slides or adequate tissue block (≤12 months prior to Day 1), collect liver biopsy sample. (Procedure may be performed within the 12 week screening window, and assuming all other Screening assessments indicate a likelihood that the subject will qualify based on biopsy).**	Clarification
Section 9.8.4, Day 1 Procedures	9.~~7~~.4. Day 1 Procedures (Randomization) • Assessment of baseline pruritus	9.**8**.4. Day1 Procedures (Randomization) • Assessment of baseline pruritus **(via medical history evaluation)** **- Thyroid hormones**	Clarification
Section 9.8.5, DB Month 1 Procedures	9.~~7~~.5. Month 1 Procedures - Metabolic parameters ~~(excluding HbA1c)~~	9.**8**.5. **DB** Month 1 Procedures - Metabolic parameters	Refer to Table 1 for changes in assessments
Section 9.8.6, DB Month 2 and Month 5 Procedures	~~9.7.6.~~ Month 2 ~~Procedures~~ ~~9.7.9.~~ Month 5 Procedures	9.**8.6. DB Month 2 and** Month 5 Procedures	Editorial
Section 9.8.7, DB Month 3 and Month 9 Procedures	9.~~7~~.7. Month 3 and Month 9 Procedures	9.**8**.7. **DB** Month 3 and Month 9 Procedures **• Health-related quality of life questionnaires and health status for the assessment of health utilities (Month 3 only)** **• Pruritus VAS (Month 3 only)** **- Metabolic parameters (including HbA1c)** **- Markers of inflammation, apoptosis, and necrosis (Month 3 only)** **- Trough PK assessment (all subjects) (Month 3 only)** **- PD assessments (all subjects) (Month 3 only)** **- Noninvasive panel of liver fibrosis (ELF, FibroMax, and Fibrometer) (Month 3 only)**	Refer to Table 1 for changes in assessments

Section 9.8.8, DB Month 4 Procedures	9.~~7~~.8. Month 4 Procedures ~~• Health-related quality of life questionnaires and health status for the assessment of health utilities~~ - Metabolic parameters ~~(excluding HbA1c)~~	9.**8**.8. DB Month 4 Procedures • **Pruritus VAS** - **Metabolic parameters**	Refer to Table 1 for changes in assessments
Section 9.8.9, DB Month 6 Procedures	9.~~7.10~~. Month 6 Procedures	9.**8.9. DB** Month 6 Procedures	Editorial
Section 9.8.10, DB Month 12/EOT/EOS	9.~~7.11~~. Month 12/EOT/EOS • Health-related quality of life questionnaires and health status for the assessment of health utilities • Liver biopsy	9.**8.10. DB** Month 12/EOT/EOS • Liver biopsy **(must be completed prior to dosing with investigational product at Day 1 OLE)**	Clarification
Section 9.7.10.1, Additional Procedures at Month 12/OLE Day 1 . . .	Section 9.~~7.11~~.1 • Record the visit in IWRS, and dispense ~~open-label~~ investigational product - To take the first dose of ~~open-label~~ investigational product the next day	Section 9.**8.10**.1 • **Review OLE ICF and obtain signatures before performing any OLE-related procedures** • **Perform EGD procedure unless data from a recent EGD (within 6 months of OLE Day 1) are available. Subjects varices will not continue in the OLE Phase.** • Record the visit in IWRS, and dispense investigational product - To take the first dose of investigational product the next day	Clarification

Section 9.8.11, OLE Month 1 *through* Section 9.8.14, OLE Month 12	*The following OLE study days have been eliminated: M15, M18, M21, and M24.* *The following assessments have been removed from the protocol:* ~~• Serum markers of inflammation, apoptosis, and necrosis – all timepoints~~ ~~• Exploratory biomarkers of disease severity – all timepoints~~ ~~• PD blood samples – all timepoints~~ ~~• Trough PK blood samples – all timepoints~~ ~~• Serial PK blood samples – all timepoints~~ ~~• Lipoprotein analysis – M3, M4, and M9~~ ~~• LiverMultiScan – all timepoints where scheduled in Version 2~~	*Note: With the elimination of M24 study day, the OLE EOT/EOS study day is now M12. Thus, all EOS procedures scheduled at M24 in Version 2 will now be performed at M12 in Version 3.* *Assessments added to the OLE study days include the following:* • **Waist and hip circumference – all timepoints** • **EGD procedure – OLE Day 1, M6, M12, ET** • **Review DILI management algorithm – all timepoints**	The changes in assessments in OLE reflect change in the OLE study period from 2 years to 1 year, and change in scope of assessments during OLE (Refer to Table 2 for changes in assessments) EGD and review of DILI management algorithm are safety procedures added to the protocol.
Section 9.7.16, Early Termination Procedures	• Health-related quality of life questionnaires (eg, patient reported outcomes) and health status for the assessment of health utilities (eg, healthcare resource use). • Pruritus VAS.	• Health-related quality of life questionnaires (eg, patient reported outcomes) and health status for the assessment of health utilities (eg, healthcare resource use) **(Double-Blind Phase only)** • Pruritus VAS **(Double-Blind Phase only).**	Clarification
Section 10.4, Investigational Product Administration	Refer to Section 9.1.	Refer to Section 9.1 **and Section 9.2**.	Clarification
Section 12.1, Liver Biopsies	Given that historical biopsies are to be obtained no more than 12 months before Day 1, slides should be sent for central reading at least 4 weeks before the end of the **6**-month window to ensure that the results are available in time for Day 1.	Given that historical biopsies are to be obtained no more than 12 months before Day 1, slides should be sent for central reading at least 4 weeks before the end of the **12**-month window to ensure that the results are available in time for Day 1.	Correction
Section 12.1.1, Central Reading of Liver Histology	Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN scoring system ~~or cryptogenic cirrhosis with metabolic factors assumed to be due to NASH~~ must be confirmed for study eligibility.	Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN scoring system must be confirmed for study eligibility.	Cryptogenic cirrhosis is no longer considered as the inclusion criteria in this protocol

<table>
<tr>
<td>Section 12.2, Child-Pugh Assessment</td>
<td>~~The CP score is used to assess the prognosis of chronic liver disease, particularly 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 1-3, with 3 indicating most severe. Chronic liver disease is classified into CP Class A to Class C as indicated in Table 4~~. CP score will be calculated according to the frequency listed in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).
~~Table 4: Child-Pugh Scoring System~~
<table>
<tr><th rowspan="2">~~Factor~~</th><th colspan="3">~~Points~~</th></tr>
<tr><th>~~1~~</th><th>~~2~~</th><th>~~3~~</th></tr>
<tr><td>~~Bilirubin (mg/dl)~~</td><td>~~<2~~</td><td>~~2-3~~</td><td>~~>3~~</td></tr>
<tr><td>~~Albumin (g/dl)~~</td><td>~~>3.5~~</td><td>~~3.5-2.8~~</td><td>~~<2.8~~</td></tr>
<tr><td rowspan="2">~~Prothrombin time (seconds prolonged) or INR~~</td><td>~~0-3~~</td><td>~~4-6~~</td><td>~~>6~~</td></tr>
<tr><td>~~<1.7~~</td><td>~~1.7-2.3~~</td><td>~~>2.3~~</td></tr>
<tr><td>~~Ascites~~</td><td>~~None~~</td><td>~~Mild~~</td><td>~~Moderate-Severe~~</td></tr>
<tr><td>~~Hepatic Encephalopathy~~</td><td>~~None~~</td><td>~~Grade 1 or 2~~</td><td>~~Grade 3 or 4~~</td></tr>
</table>
~~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). This level has been the accepted criterion for listing for liver transplantation (Pugh 1973, Lucey 1997).~~</td>
<td>CP score will be calculated as described in Section 7.4.3.1 and according to the frequency listed in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).</td>
<td>The information in this section is redundant with Section 7.4.3.1.</td>
</tr>
</table>

Section 12.3, 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 decompensation7.4.3.2 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 results 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. MELD scores will be calculated based on creatinine, bilirubin, INR, and sodium values as appropriate, collected at the same visit with modification by United Network for Organ Sharing. If only 1 component of MELD needs to be repeated, all other components should also be repeated. INR will be calculated based on PT value by the central laboratory.~~ ~~MELD score will be calculated~~ according to the frequency listed in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).	MELD score **will be calculated as described** in **Section 7.4.3.2** and according to the frequency listed in Table 1 (Double-Blind Phase) and Table 2 (OLE Phase).	The information in this section is redundant with Section 7.4.3.2.

Section 12.5, Patient-Reported Outcomes and Healthcare Resource Use	~~• Short Form Health Survey (SF-36): The SF-36 is a 36-item, self-report measure designed to assess the quality of life in patients (Ware 2000).~~ ~~These may require transcription to the eCRF by study site staff.~~ ~~Healthcare resource use will be collected from eCRFs including number, reason for and duration of hospitalizations and emergency room visits, number of outpatient physician visits (patient reported), and use of concomitant medications. The purpose is to evaluate the effects of OCA compared to placebo on patient-reported outcomes and healthcare resources.~~		The patient reported outcome instrument SF-36 will not be used to evaluate health-related quality of life in this study. Deleted since this level of details is not necessary in a protocol.
Section 12.6.3,	At investigational sites where the device is available, TE using the Fibroscan instrument (Echosens, Paris, France), ~~LiverMultiScan technology (Perspectum Diagnostics, Oxford, United Kingdom), or MRE,~~ to assess liver fibrosis will be conducted by staff who are trained in the use and data interpretation of the device. Assessments will be performed according to the schedule presented in Table 1 ~~(~~Double-Blind Phase~~) and Table 2 (OLE Phase)~~. ~~Whichever modality/ies used at baseline must be collected consistently at each visit.~~	At investigational sites where the device is available, TE using the Fibroscan instrument (Echosens, Paris, France), to assess liver fibrosis will be conducted by staff who are trained in the use and data interpretation of the device. Assessments will be performed according to the schedule presented in Table 1 **during the** Double-Blind Phase **only. MRE will be assessed only in subjects who had a baseline MRE already performed.**	LiverMultiScan and MRE assessments have been removed from the protocol.
Section 12.7, Efficacy Laboratory Assessments	(Section 15.2.7) ~~Homeostatic model assessment – insulin resistance (~~HOMA-IR~~)~~ values will be calculated based on glucose and insulin concentrations.	*The following text was moved from Section 15.2.7 to Section 12.7* **HOMA-β and** HOMA-IR values will be calculated based on glucose and insulin concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.	HOMA-β has been added to the protocol.

Section 13.1, Pharmacokinetic Blood Sampling	An assessment of steady-state exposures (on an aggregate level) will be performed by an internal Intercept clinical pharmacologist/ pharmacometrician who is discrete from the study team. Subjects participating in serial PK assessments will provide blood samples for measurement of OCA and its conjugates (glyco-OCA and tauro-OCA) ~~0.5 hour prior to administration of investigational product (predose). Subjects will then receive a dose of investigational product with approximately 240 mL of water~~. ~~During the OLE Phase:~~ ~~• Subjects who agree to participate in the Serial PK assessments will have samples obtained at Month 1, Month 4, and Month 24 OLE.~~ ~~• Trough PK samples will be obtained from all subjects prior to dose administration on Months 1, 2, 3, 4, 5, 6, 12, 18, 24 OLE, and ET.~~	An assessment of steady-state exposures (on an aggregate level) will be performed by an internal Intercept clinical pharmacologist/ pharmacometrician **or designee** who is discrete from the study team. Subjects participating in serial PK assessments will provide blood samples for measurement of OCA and its conjugates (glyco-OCA and tauro-OCA). **Subjects should be reminded to fast for at least 8 hours prior to the PK assessment; although water is allowed during the fasting period. If the subject reports having eaten within the fasting period, this will be documented in the source and the eCRF; however, the PK assessment will still be conducted.** **Subjects will then receive a dose of investigational product with approximately 240 mL of water.**	Clarifications PK assessments during the OLE Phase have been removed
Section 13.3, Bioanalysis		*The following text was moved from Section 15.2.7 to Section 13.3* Total OCA will be calculated based on OCA, tauro-OCA, and glyco OCA concentrations.	Editorial

Section 14.3, Microbiome/ Metabolome Analysis	~~14.3. Microbiome/Metabolome Analysis~~ ~~Stool specimens collected for microbiome/metabolome analyses will be collected from all subjects at US sites. Specimens will undergo microbiota 16S ribosomal RNA gene analysis, genome testing, fecal metabolomics, fecal bile acid analysis, and other appropriate assays to determine if and how OCA influences the composition and activity of the resident microbiota in the gastrointestinal tract. Subjects will be provided kits and instructions for collection of stool specimens at home, as appropriate.~~ ~~Microbiome/metabolome analyses will be assessed in subjects according to the schedule presented in Table 1 (Double-Blind Phase).~~	*This section has been deleted from Version 3*	Microbiome/metabolome assessments have been removed from the study.
Section 14.3.1, Exploratory Biomarkers of Disease Severity	[redacted]		Clarifications
Section 15.1.1.1, Adverse Event		**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.**	Additional safety procedure added to the protocol.

Section 15.1.3, Relationship to Study Procedures	Table 7: Relationship of Adverse Events Study Procedures	Table 7: Relationship of Adverse Events **to Liver Biopsy and Other** Study Procedures	Clarification
Section 15.1.4.1, Severity of Pruritus (as an Adverse Event)	Per Section 8.2.1.2, subjects with pruritus ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product must discontinue investigational product but are encouraged to continue study visits	Per Section 8.2.1.2, subjects with pruritus ≥Grade 3 in severity **(per CTCAE)** and possibly, probably, or definitely related to investigational product must discontinue investigational product but are encouraged to continue study visits	Clarification
Section 15.1.5.1, Reporting of Adverse Events	Redacted medical record source documentation will be requested for all SAEs ~~and emergency room visits~~.	**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.** Redacted medical record source documentation will be requested for all SAEs.	Additional safety procedure added to the protocol.
Section 15.1.7, Additional Investigator Responsibilities for SAEs	The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the subject's AE ~~EDC~~.	The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the subject's AE **eCRF**.	Editorial
Section 15.1.9, Notification of Post-Study SAEs	~~If an Investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, the Sponsor should be notified immediately (ie, within 24 hours) by following the instructions provided in Section .~~		Clarification
Section 15.1.10, Follow-Up of AEs and SAEs	All subjects showing possible drug-induced liver injury should be followed until all abnormalities return to normal or to the baseline state.	All subjects showing possible drug-induced liver injury **or disease progression** should be followed until all abnormalities return to normal or to the baseline state. **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.**	Additional safety procedure added to the protocol.

Section 15.1.11, Pregnancy and Follow-Up	Thereafter, the subject and infant must be followed as considered appropriate by the Investigator and the Sponsor.	Thereafter, the subject and infant must be followed as considered appropriate by the Investigator and **any new updates should be sent to** the Sponsor.	Clarification
Section 15.2.1, Medical History/ Demographics	Baseline pruritus by severity will be obtained on Day 1.	Baseline pruritus by severity will be obtained on Day 1 **using the Pruritus VAS questionnaire**.	Clarification

<table>
<tr>
<td>Section 15.2.7, Laboratory Assessments</td>
<td>
The following text was moved from Section 15.2.7 to Section 13.3 or 14.4.2
All exploratory biomarkers of disease severity and blood samples collected will be stored for up to 1 year after the end of the study and destroyed if not analyzed.
Homeostatic model assessment – insulin resistance (HOMA-IR) values will be calculated based on glucose and insulin concentrations.
Total OCA will be calculated based on OCA, tauro-OCA, and glyco OCA concentrations.
Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.
Table 12
<table>
<tr><th>Laboratory Assessment (Phase)</th><th>Scores and Analytes[a]</th></tr>
<tr><td>Metabolic parameters (Double-Blind and OLE)</td><td>Fasting plasma glucose, insulin, C-peptide, HbA1c, and HOMA-IR</td></tr>
<tr><td>~~Microbiome/Metabolome Analysis (Double Blind only)~~</td><td>~~Microbiota 16S ribosomal RNA gene analysis, genome testing, fecal metabolomics, fecal bile acid analysis, and other appropriate assays to determine if and how OCA influences the composition and activity of the resident microbiota in the gastrointestinal tract~~</td></tr>
<tr><td>~~Genetics analysis (Double-Blind and OLE)~~</td><td>~~DNA and RNA analysis for nucleotide polymorphisms that may be involved in NASH~~</td></tr>
</table>
In Table 10, the OLE Phase was deleted from the following laboratory assessments: lipoprotein analysis, markers of inflammation, apoptosis, necrosis, PD assessment, PK analytes (Trough PK), Exploratory biomarkers of disease severity, and PK analytes.
</td>
<td>
Table 12
<table>
<tr><th>Laboratory Assessment (Phase)</th><th>Scores and Analytes[a]</th></tr>
<tr><td>Metabolic parameters (Double-Blind and OLE)</td><td>Fasting plasma glucose, insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR</td></tr>
<tr><td>Cardiovascular risk scores</td><td>FRS, Reynolds score, and SCORE</td></tr>
<tr><td>PK analytes (Serial PK; Double-Blind)</td><td>OCA, tauro-OCA and glyco-OCA and possible other conjugates or metabolites not yet identified</td></tr>
</table>
</td>
<td>This text is moved to other sections of Version 3 for clarity</td>
</tr>
<tr>
<td>Section 15.2.8, Pruritus Assessment</td>
<td>15.2.8. ~~Health-Related Quality of Life~~</td>
<td>15.2.8. Pruritus Assessment</td>
<td>Editorial change</td>
</tr>
</table>

Section 16.5.2, Clinical Outcomes		**Analyses of the clinical outcomes composite endpoint and individual components of outcome events will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo**. **Only adjudicated events will be included in analyses. Subjects with none of these events will be censored at the date of last contact.**	Clarifications
Section 16.11, Safety Analyses	Safety evaluations will comprise treatment-emergent AEs, adjudicated CV events, vital signs, electrocardiograms (ECGs), pruritus VAS, and clinical laboratory results.	Safety evaluations will comprise treatment-emergent AEs, **AEs of special interest including pruritus and hepatic safety**, adjudicated CV events, vital signs, electrocardiograms (ECGs), pruritus VAS, and clinical laboratory results.	Clarification

Section 16.5.1 Other Histology Endpoints	o Ishak scoring criteria from Baseline to Month 12 - Improvement to Stage 4 o Laennec staging system from Baseline to Month 12 - Improvement to Stage 3 • Percentage of subjects with no worsening of fibrosis using the following criteria: o Ishak (if baseline Ishak stage <6) o Laennec staging system (if baseline Laennec stage <4C) • Percentage of subjects with progression of fibrosis using the following criteria: o Ishak (if baseline Ishak stage <6) o Laennec staging system (if baseline Laennec stage <4C) [redacted] • Percentage of subjects with improvement in each component of NAS (steatosis, lobular inflammation, and hepatocellular ballooning) • Changes in NAS • Changes in SAF score Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and cryptogenic cirrhosis [yes/no]. The change in NAS, SAF, and PCA will be analyzed using an ANCOVA model at each visit with change from baseline as the dependent variable including treatment group and randomization	o Ishak scoring criteria from Baseline to Month 12 - Improvement to Stage 4 **or lower** o Laennec staging system from Baseline to Month 12 - Improvement to Stage 3 **or lower** • Percentage of subjects with no worsening **(includes improvement)** of fibrosis using the following criteria: o Ishak **scoring criteria** (if baseline Ishak stage <6) **from Baseline to Month 12** o Laennec staging system (if baseline Laennec stage <4C) **from Baseline to Month 12** • Percentage of subjects with progression of fibrosis using the following criteria: o Ishak **scoring criteria** (if baseline Ishak stage <6) **from Baseline to Month 12** o Laennec staging system (if baseline Laennec stage <4C) **from Baseline to Month 12** • Change in morphometric assessment of quantitative collagen **from Baseline to Month 12** (assessed as PCA) • Percentage of subjects with improvement in each component of NAS (steatosis, lobular inflammation, and hepatocellular ballooning) **from Baseline to Month 12** • Changes in NAS **from Baseline to Month 12** • Changes in SAF score **from Baseline to Month 12** Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and cryptogenic cirrhosis [yes/no]. The change in NAS, SAF, and PCA will be analyzed using an **analysis of covariance (**ANCOVA) model at each visit with change from baseline as the dependent variable including treatment group and randomization	Clarification

	stratification factor as fixed effects and baseline as a covariate.	stratification factor as fixed effects and baseline as a covariate.	
Section 16.5.2, Clinical Outcomes	• MELD score ≥15 ~~(if MELD ≤12 at Baseline)~~ • Liver transplant ~~(if MELD <15 at Baseline)~~ The percentage of subjects who reported any adjudicated events will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] ~~and cryptogenic cirrhosis [yes/no]~~).	• MELD score ≥15 • Liver transplant The percentage of subjects who reported any adjudicated events will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no].	The outcomes have been updated per study objectives and exclusion of subjects with MELD score >12.
Section 16.5.4, Metabolic Parameters	Metabolic parameters include fasting glucose, fasting insulin, C-peptide, HbA1c, and HOMA IR.	Metabolic parameters include fasting glucose, fasting insulin, C-peptide, HbA1c, **HOMA-**β, and HOMA IR.	HOMA-β assessment added to the study
Section 16.5.6, Health-Related Quality of . . .	Health-Related Quality of Life endpoints derived from the following patient-reported outcomes will be summarized by treatment group: CLDQ-NAFLD, EQ-5D-5L, WPAI, ~~and the SF-36~~. *The following statement was deleted from Sections 16.5.6, 16.5.6.1, 16.5.6.2, and 16.5.7:* ~~Further details regarding analyses will be specified in the SAP.~~	Health-Related Quality of Life endpoints derived from the following patient-reported outcomes will be summarized by treatment group: CLDQ-NAFLD, EQ-5D-5L, **and** WPAI.	SF-36 will not be used to evaluate health-related quality of life in this study. Clarification
Section 16.5.6.2, Noninvasive Radiological Assessment of Liver Fibrosis	16.5.~~7.3~~. Noninvasive Radiological Assessment of Liver Fibrosis Noninvasive radiological assessments of liver fibrosis include TE using the Fibroscan TE device~~, liver magnetic resonance imaging (using LiverMultiScan), and liver MRE~~.	16.5.**6.2**. Noninvasive Radiological Assessment of Liver Fibrosis Noninvasive radiological assessments of liver fibrosis include TE using the Fibroscan TE device.	LiverMultiScan and MRE assessments have been removed from the study.
Section 16.8, PK/PD Analysis		**Results from these analyses will be reported separate from the clinical study report.**	Clarifications
Section 16.10, Examination of Subgroups *and* Section 16.11.3	~~Further details regarding subgroups analyses will be specified in the SAP.~~		Clarification

Section 16.11, Safety Analyses	Safety evaluations will comprise treatment-emergent AEs, adjudicated CV events, vital signs, electrocardiograms (ECGs), and clinical laboratory results.	Safety evaluations will comprise treatment-emergent AEs, adjudicated CV events, vital signs, electrocardiograms (ECGs), **pruritus VAS**, and clinical laboratory results.	Clarification
Section 16.11.1, Adverse Events		**Adverse events of special interest, to be specified in the SAP, will be summarized for each treatment group**.	Clarification
Section 16.12.1, Safety Analyses (OLE)	~~Similar analyses to those are described above~~ will be conducted for the OLE.	**Safety evaluations conducted during the Double-Blind Phase** will **also** be conducted for the OLE.	Editorial
Section 16.12.2, Efficacy Analyses (OLE)	~~16.12.2. Efficacy Analyses (OLE)~~ ~~Efficacy analyses conducted during the Double-Blind Phase will be repeated during the OLE. Separate summaries will be presented by the randomized treatment assignment in the double blind phase. For subjects with optional biopsy in OLE, histological changes will be assessed.~~	*This section has been deleted in Version 3.*	Any efficacy analyses during OLE is not specified in the protocl due to scaled-back assessments during the OLE Phase. Further details may be included in SAP.
Section 16.13, Data Monitoring Committee	An independent data monitoring committee (DMC) ~~that includes~~ hepatologists, pharmaceutical physicians, epidemiology/cardiology expert(s), and statistician(s) The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review PK, safety and efficacy data as well as the adjudication assessments from the ~~3~~ adjudication committees listed in Section 16.14.	An independent data monitoring committee (DMC) **will include** hepatologists, pharmaceutical physicians, epidemiology/cardiology **expert(s), DILI** expert(s), and statistician(s) The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review PK, safety and efficacy data as well as the adjudication assessments from the **2** adjudication committees listed in Section 16.14.	Clarifications

Section 22, List of References	~~Ware JE. SF-36 Health Survey Update. Spine. 2000 25 (24: 3130-3139~~. Younossi ~~Z~~, Younossi I, ~~Huong T~~, et al. Development and Validation of Disease-Specific Health Related Quality (HRQL) Instrument for Patients with Non-alcholic Fatty Liver Disease (NAFLD) and Non-alchoholic Steatohepatitis (NASH): The CLDQ-NAFLD. Hepatology. 2016 64 (1), 118A.	Younossi **ZM**, Younossi I, **Pham, HT**, et al. Development and Validation of Disease-Specific Health Related Quality (HRQL) Instrument for Patients with Non-alcholic Fatty Liver Disease (NAFLD) and Non-alchoholic Steatohepatitis (NASH): The CLDQ-NAFLD. Hepatology. 2016 64 (1), 118A. **Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715-35.**	Editorial changes

APPENDIX D. SUMMARY OF CHANGES: PROTOCOL VERSION 1.0 TO PROTOCOL VERSION 2.0 (DATED: 17 MAY 2017)

Rationale and Summary of Changes

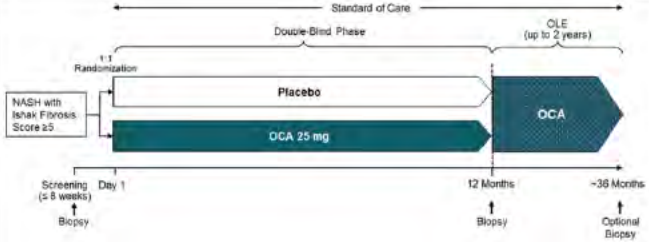
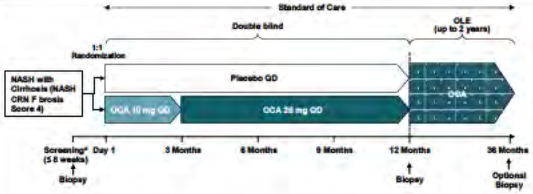
The following revisions were made to Protocol Version 1.0. Each revision also includes a reason or justification for the change. The text deleted from Protocol Version 1.0 is crossed out and revised text in Version 2.0 is indicated in bold font in the table below. Minor changes including typos or editorial revisions are not listed individually in the summary table below.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Study Personnel Contact Information	~~b~~ [redacted]	[redacted] **MD** [redacted] **Drug Safety** **Intercept Pharmaceuticals, Inc. (Intercept)** [redacted]	Organization change
Study Personnel Contact Information	~~**Clinical Operations and Project Management**~~ ~~**Contact:**~~ [redacted] [redacted] ~~Clinical Operat~~ ~~Intercept~~ ~~Telephone:~~ ~~Mobile:~~ ~~Fax:~~ ~~Email:~~ [redacted]	Deletion	Organization change
Synopsis	Approximately ~~75 to 100~~ investigational sites, globally.	• Approximately **150** investigational sites, globally.	Additional number of sites added to ensure enrollment feasibility.
Synopsis Primary Objectives	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage using ~~Ishak s~~coring ~~criteria~~ from Baseline to Month 12	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage using **the Nonalcoholic Steatohepatitis**	NASH CRN criteria were developed specifically for the NAFLD population (histological assessment in patients with fibrosis and

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
		(NASH) Clinical Research Network (CRN) scoring **system** from Baseline to Month 12	cirrhosis secondary to NASH)
Synopsis Secondary Objectives Section 6.2 Secondary Objectives	~~Key~~ Secondary Objectives: To evaluate the effects of OCA treatment compared with placebo on: [redacted] Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least ~~1 stage using Nonalcoholic Steatohepatitis (NASH) Clinical Research Network (CRN)~~ scoring ~~system~~ from Baseline to Month 12	Secondary Objectives: To evaluate the effects of OCA treatment compared with placebo on: • Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least **2** stages using **Ishak** scoring **criteria** from Baseline to Month 12	Morphometric assessment moved to exploratory endpoint because it is not a validated assessment and the magnitude of change that may be clinically meaningful is not well-established. Therefore, this endpoint has been moved from a key secondary endpoint to further down in the hierarchy. Instead, improvement assessed using the modified Ishak score (adapted to NASH) will be moved up as the key secondary endpoint. To ensure that a clinically significant magnitude of change is assessed, this endpoint will evaluate an improvement by 2 points or more.
Synopsis Secondary Objective Section 6.2 Secondary Objectives	• All-cause mortality and liver-related clinical outcomes ~~as measured by the time to first occurrence of any~~ of the following adjudicated events (clinical outcomes composite endpoint): • ~~Time to occurrence of liver-related death~~	• **Occurrence of** all-cause mortality and liver-related clinical outcomes of the following adjudicated events (clinical outcomes composite endpoint): • **Occurrence of individual components of outcome events**	Clarification of analysis of adjudicated clinical outcomes, including both time-to-event analysis and incidence.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Synopsis ~~Additional Secondary Objectives Section~~ ~~6.3 Additional Secondary Objectives~~	Synopsis ~~Additional Secondary Objectives Section~~ ~~6.3 Additional Secondary Objectives~~	Deletion	Key secondary and additional objectives were combined under Secondary Objectives
Synopsis Secondary Objectives Section 6.2 Secondary Objectives	Insertion	[redacted]	This endpoint was moved from key secondary to an additional secondary objective.
Synopsis Secondary Objectives Section 6.2 Secondary Objectives	To evaluate the effects of OCA treatment compared with placebo on: • Histological changes in fibrosis including improvement, no worsening, and progression from Baseline to Month 12 using the following criteria, as appropriate: ~~Ishak scoring criteria~~ ~~NASH CRN criteria~~ Laennec staging system	To evaluate the effects of OCA treatment compared with placebo on: • Histological changes in fibrosis including improvement, no worsening, and progression from Baseline to Month 12 using the following criteria, as appropriate: – **NASH CRN scoring system** – **Ishak scoring criteria** – Laennec staging system	Primary and secondary objectives were reordered, which affected the order of the additional secondary objectives.
Synopsis Secondary Objectives Section 6.2 Secondary Objectives	• ~~Liver histology by morphometric assessment of percent fat at Month 12~~	**Deletion**	This assessment is considered unnecessary for the study.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Synopsis Methodology Section 7.1 Overall Study Design	This Phase 3, double-blind, randomized, placebo-controlled, multicenter international study will evaluate the efficacy and safety of OCA in subjects with a biopsy-confirmed diagnosis of cirrhosis (~~Ishak fibrosis score ≥5 [incomplete, probable, or definitive cirrhosis]~~) due to NASH ~~(or cryptogenic cirrhosis with evidence of metabolic syndrome)~~ determined by central reading of liver histology. Subjects with hepatic decompensation or CP Class B or Class C cirrhosis are excluded. ~~All histology assessments will be performed centrally.~~ **Double-Blind Phase (12 Months):** Subjects will be screened for a period of up to 8 weeks before entering the study. Subjects who meet the entry requirements will be randomized in a 1:1 ratio to receive placebo or OCA 25 mg daily in conjunction with local standard of care. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no) ~~and by Ishak fibrosis stage (Ishak fibrosis 5 or 6)~~. Investigational product (ie, OCA or placebo) will be taken orally, with water, once daily. ~~S~~afety and laboratory assessments will be evaluated at clinical visits at Day 1, ~~Month 1, and once every 3 months following the initiation of treatment (Day 1) through~~ Month 12. **Open-Label Extension (up to 24 Months):** Subjects who complete the Double-Blind Month 12 Visit are eligible to enroll into the OLE for the evaluation of safety. All subjects will receive OCA upon entry into the OLE. Subjects will continue the same dosing regimen they received at the end of the Double-Blind Phase.	This Phase 3, double-blind, randomized, placebo-controlled, multicenter international study will evaluate the efficacy and safety of OCA in subjects with a biopsy-confirmed diagnosis of cirrhosis (**based on fibrosis score of 4 using NASH CRN scoring system**) due to NASH determined by central reading of liver histology. **Up to approximately 30% of total enrolled subjects may have a diagnosis of cryptogenic cirrhosis and presence of metabolic risk factors**. Subjects with hepatic decompensation or CP Class B or Class C cirrhosis are excluded. **Subjects who progress to CP Class B or Class C during the study will discontinue investigational product, but should be encouraged to continue study visits**. Double-Blind Phase (12 Months): Subjects will be screened for a period of up to 8 weeks before entering the study. Subjects who meet the entry requirements will be randomized in a 1:1 ratio to receive placebo or OCA daily in conjunction with local standard of care. **Subjects will receive OCA 10 mg for the first 3 months**. **At Month 3, all subjects will titrate to OCA 25 mg once daily unless there are safety concerns.** Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no**) and cryptogenic cirrhosis (yes or no)**. Investigational product (ie, OCA or placebo) will be taken orally, with water, once daily**. Efficacy, s**afety and laboratory assessments will be evaluated at clinical visits at Day 1, **monthly for the initial 6 months (Month 1 through Month 6 Visits), Month 9,** and Month 12.	Up to 30% of subjects with cryptogenic cirrhosis will be included in the study as a significant proportion of patients with cirrhosis due to NASH may lose their characteristic histologic features of NASH and may present as cryptogenic cirrhosis based on histopathology. However, it is not known whether these patients will have a different response compared to those with clear histologic features of NASH, no more than 30% of subjects with cryptogenic cirrhosis will be included. Subjects who progress to Child Pugh Class B or C will be discontinued from the study as they may exhibit moderate to severe hepatic impairment, and are likely to result in increased serum concentrations of OCA. Since optimal dosing for NASH subjects with hepatic impairment has not yet been determined, these subjects will discontinue IP. The 10 mg dose titration at Month 3 provides adequate time to lower endogenous

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
		Open-Label Extension (up to 24 Months): Subjects who complete the Double-Blind Month 12 Visit are eligible to enroll into the OLE for the evaluation of safety. All subjects will receive OCA upon entry into the OLE. **Subjects who received placebo during the Double-Blind phase will receive OCA 10 mg daily for 3 months and titrate to OCA 25 mg daily in the same manner that was applied during the Double-Blind phase**. Subjects **who received OCA during the Double-Blind Phase** will continue the same dosing regimen they received at the end of the Double-Blind Phase.	bile acid levels, while establishing safety and tolerability. Assessment of PK will be conducted at both 10 and 25 mg to ensure exposure is within safe and tolerated ranges. For monthly 6 month assessment: it will allow for additional safety monitoring during study initiation, including adverse events and even disease progression.
Synopsis Study Design Diagram Section 7.1. Overall Study Design			Study design figure updated to include the 10 mg titration for 3 months prior to dose titration and the description of the patient population was updated to include cryptogenic cirrhosis.
Synopsis Study Design Diagram Footnote Section 7.1.1 Study Design Diagram	Note: Subjects with ~~NASH and an Ishak fibrosis score ≥5 (incomplete, probable, or definitive cirrhosis)~~ will be enrolled in the study. Subjects with CP Class B or CP Class C cirrhosis are excluded. Subjects without a liver biopsy obtained ~~≤6~~ months prior to Day 1 will have a biopsy at Screening Visit 2.	**Note: Subjects with cirrhosis (based on a NASH CRN fibrosis score 4) due to NASH or cryptogenic cirrhosis with metabolic factors assumed to be due to NASH will be enrolled in the study.** Subjects with CP Class B or CP Class C cirrhosis are excluded. a **Two screening visit assessments will be performed at least 4 weeks apart. Screening Visit 1 will occur 8 weeks prior to Day 1, and Screening Visit 2 will occur 4 weeks ± 2 days prior to Day 1. Subjects without a liver biopsy obtained ≤12 months**	Inclusion criteria were modified and updated in the footnote and clarification on the dose titration schedule is provided.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
		prior to Day 1 will have a biopsy at Screening Visit 2. **b During the double-blind period, all subjects will titrate to OCA 25 mg (or matching placebo) at Month 3 unless safety concerns dictate otherwise. A blinded review of Month 1 and Month 2 safety data, including liver biochemistry and adverse events by the medical monitor will be conducted prior to a subject's Month 3 visit.** **c All subjects who enroll into the OLE will receive OCA. Subjects randomized to placebo in the Double-Blind Phase will initiate investigational product of OCA 10 mg for the first 3 months of the OLE prior to uptitrating to OCA 25 mg. Uptitration will be based on safety and tolerability assessments completed at Month 1, Month 2, and Month 3 of the OLE. Subjects randomized to OCA will continue the same dosing regimen they received at the end of the Double-Blind Phase.** **d The study will remain blinded until all subjects complete the double-blind Phase. To maintain blinding, all placebo, OCA 10 mg, and OCA 25 mg tablets and bottles will be identical. Once all subjects have titrated to the 25 mg dose in the OLE, subjects may receive investigational product with an open-label identifying the product as OCA 25 mg.**	

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Synopsis Inclusion Criteria Section 8.1.1 Subject Inclusion Criteria	2.Subjects with confirmed diagnosis of NASH with ~~an Ishak fibrosis score ≥5~~ determined by central reading of a liver biopsy obtained no more than ~~6~~ months before Day 1, OR Subjects with cryptogenic cirrhosis assumed to be due to NASH as determined by central reading of a liver biopsy obtained no more than ~~6~~ months before Day 1 ~~with metabolic syndrome~~ accompanied by ~~any~~ of the following risk factors: – Obesity (body mass index ≥30 kg/m^2) – Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test, or random plasma glucose ≥200 mg/dL) – Abdominal obesity (waist circumference >102 cm [>40 in] for men and >88 cm [>35 in] for women) – Dyslipidemia (triglyceridemia ≥150 mg/dL and low high-density lipoprotein [<40 mg/dL in men and <50 mg/dL in women]) ~~– Prehypertension or hypertension (blood pressure ≥130/≥85 mmHg)~~	2. Subjects with confirmed diagnosis of **NASH with a fibrosis score of 4 based** on **NASH CRN scoring** system determined by central reading of a liver biopsy obtained no more than **12** months before Day 1, OR Subjects with cryptogenic cirrhosis assumed to be due to NASH as determined by central reading of a liver biopsy obtained no more than **12** months before Day 1 accompanied by **TWO** of the following risk factors – Obesity (body mass index ≥30 kg/m^2) – Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c ≥6.5%, fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test, or random plasma glucose ≥200 mg/dL) **or on any prescription glucose-lowering agent for Type 2 diabetes** – Abdominal obesity (waist circumference >102 cm [>40 in] for men and >88 cm [>35 in] for women) **with no evidence of ascites by imaging unless obvious on physical exam** – Dyslipidemia (triglyceridemia ≥150 mg/dL and low high-density lipoprotein [<40 mg/dL in men and <50 mg/dL in women]) **or using a prescription lipid-lowering medication due to dyslipidemia**	Updated with NASH CRN criteria because these are considered more appropriate for the study population and the primary endpoint is based on NASH CRN criteria. The window of historic biopsy changed from 6 months to 12 months before Day 1 because the NASH CRN fibrosis score of a cirrhotic patient is unlikely to improve to a lower fibrosis score within 12 months, if all other entry criteria are met. The number of qualifying criteria for identifying cryptogenic cirrhosis subjects was increased to ensure the etiology of cryptogenic cirrhosis is NASH. Prehypertension or hypertension is not considered as part of qualifying criteria for defining cryptogenic cirrhosis by the FDA and therefore was removed.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Synopsis Exclusion Criteria Section 8.1.2 Subject Exclusion Criteria	Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization. Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment: 1. Current or past history of hepatic decompensation such as ascites (~~identified on physical exam~~), variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes 4. Aspartate transaminase ~~>7~~× upper limit of normal (ULN) 5. Alanine aminotransferase ~~>7~~× ULN 7.Platelet count ~~≤75,000~~/mm^3 at Screening 11. Creatine phosphokinase >~~5~~× ULN 28. Previous exposure to OCA	Criteria with exclusionary laboratory values are to be based on the most recent laboratory result available prior to randomization. Subjects who satisfy any of the following exclusion criteria will be ineligible for enrollment: 1. Current or past history of hepatic decompensation such as **clinically significant** ascites **(requiring medical intervention**), variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy (Grade I or greater based on West Haven classification), or hepatorenal/hepatopulmonary syndromes 4. Aspartate transaminase ≥**5**× upper limit of normal (ULN) 5. Alanine aminotransferase ≥**5**× ULN 7. Platelet count ≤**100000**/mm^3 at Screening 11. Creatine phosphokinase >**3**× ULN 28. Previous exposure to OCA **within 12 months**	The threshold of the exclusion criteria for AST and ALT were lowered to ≥5x ULN to exclude subjects with significantly high aminotransaminases at study entry. The exclusion criterion for platelet counts was modified to ≤100000/mm^3 to further ensure subjects enrolled in the study are well compensated. The exclusion criterion for creatine phosphokinase was revised to >3x ULN because CPK >3x ULN is consider too high. Due to limited hepatocellular reserve, cirrhotic patients might have advanced liver failure with relatively less elevated, even normal transaminase levels. For this reason, ALT and AST exclusion criteria were modified to exclude subjects with significant worsening of ALT and AST.
Synopsis Liver Histology and	*Central Reading of Liver Histology:* All biopsy assessments will be performed centrally, including assessments of biopsies to determine study eligibility.	*Central Reading of Liver Histology:* All biopsy assessments will be performed centrally, including assessments of biopsies to determine	Order of the assessments was changed.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Event Adjudication and Data Monitoring Committee Oversight:	Histological presence of NASH with ~~an Ishak fibrosis score ≥5~~ or cryptogenic cirrhosis assumed to be due to NASH must be confirmed for study eligibility. For each biopsy, fibrosis will be graded in accordance with ~~Ishak~~ scoring system ~~(Ishak 1995)~~. -In addition to the primary scoring ~~of Ishak~~, biopsy samples will also be scored based on the ~~NASH CRN criteria~~ (~~Kleiner 2005~~), Laennec staging (Wang 2015), and SAF scoring (Bedossa 2014), and for quantitative collagen~~ and percent fat~~.	study eligibility. Histological presence of NASH with **a fibrosis score of 4 based on NASH CRN scoring system** or cryptogenic cirrhosis **with metabolic factors** assumed to be due to NASH must be confirmed for study eligibility. For each biopsy, fibrosis will be graded in accordance with **NASH CRN** scoring system (**Kleiner 2005**). In addition to the primary scoring **using** NASH CRN **scoring system**, biopsy samples will also be scored based on the **modified Ishak** scoring criteria **(Ishak 1995)**, Laennec staging (Wang 2015), and SAF scoring (Bedossa 2014), and for quantitative collagen.	
Synopsis Liver Histology and Event Adjudication and Data Monitoring Committee Oversight:	*DMC Oversight:* An independent DMC will review all safety and efficacy data resulting from the study at periodic intervals.	*DMC Oversight:* An independent DMC will review all safety and efficacy data resulting from the study at periodic intervals. **In addition, PK exposure data will be available, if needed**.	PK data will be available to the DMC for additional safety monitoring purposes.
Synopsis Investigational Product, Dosage and Mode of Administration	OCA tablet, 25 mg, once daily, oral administration	OCA tablet, **10 mg or** 25 mg, once daily, oral administration	Added to allow dose titration
Synopsis Criteria for Evaluation	Histological improvement of fibrosis using ~~Ishak~~ Endpoint: Improvement in fibrosis by at least 1 stage using ~~Ishak~~ scoring ~~criteria~~ from Baseline to Month 12	Histological improvement of fibrosis using **NASH CRN scoring system**	Updated with NASH CRN criteria because the primary endpoint using the NASH

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Section 11 Overview of Assessments		Endpoint: Improvement in fibrosis by at least 1 stage using **NASH CRN** scoring **system** from Baseline to Month 12	CRN criteria are considered more appropriate for this population.
Synopsis Criteria for Evaluation Section 11 Overview of Assessments	Liver histology by morphometric assessment of quantitative collagen [redacted] Histological improvement in fibrosis using ~~NASH CRN~~ Endpoint: Improvement in fibrosis by at least ~~1~~ stage using ~~NASH CRN~~ scoring system from Baseline to Month 12 Clinical outcomes Endpoint: ~~Time to first~~ occurrence of any of the following adjudicated events: ~~Liver related death~~ ~~Endpoint: Time to occurrence of liver related death~~	Liver histology by morphometric assessment of quantitative collagen [redacted] Histological improvement in fibrosis using **Ishak scoring criteria** Endpoint: Improvement in fibrosis by at least **2** stage**s** using **the** ~~NASH CRN~~ **Ishak scoring criteria** from Baseline to Month 12 Clinical outcomes Endpoint: **O**ccurrence of any of the following adjudicated events: **Individual components of outcome events** Endpoint: **Occurrence of individual components of outcome event**s	Morphometric assessment moved to exploratory endpoint because it is not a validated assessment and the magnitude of change that may be clinically meaningful is not well-established. Therefore, this endpoint has been moved from a key secondary endpoint to further down in the hierarchy. Instead, improvement assessed using the modified Ishak score (adapted to NASH) will be moved up as the key secondary endpoint. To ensure that a clinically significant magnitude of change is assessed, this endpoint will evaluate an improvement by 2 points or more.
Synopsis Criteria for Evaluation Section 11 Overview of Assessments	~~Additional~~ Secondary Objectives Histological change in fibrosis (improvement, no worsening, and progression, as appropriate) Endpoint: Change in ~~Ishak scoring criteria~~ from Baseline to Month 12 Change in ~~NASH CRN criteria~~ from Baseline to Month 12	Secondary Objectives Histological change in fibrosis (improvement, no worsening, and progression, as appropriate) Endpoint: Change in **NASH CRN scoring system** from Baseline to Month 12 Change in **Ishak scoring criteria** from Baseline to Month 12	Order modified.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Synopsis Criteria for Evaluation Section 11 Overview of Assessments	~~Key~~ Secondary Objectives Liver histology by morphometric assessment of quantitative collagen Endpoint: [redacted]	Secondary Objectives Liver histology by morphometric assessment of quantitative collagen Endpoint: [redacted]	Specified instruction will be provided in the histology manual.
Synopsis Enrollment and Randomization	A total of approximately 360 subjects will be enrolled and randomized into the study in a 1:1 ratio to placebo or OCA ~~25 mg~~. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no)~~ and fibrosis (Ishak fibrosis score 5 or 6~~).	A total of approximately 360 subjects will be enrolled and randomized into the study in a 1:1 ratio to placebo or OCA. Randomized subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no) and **cryptogenic cirrhosis (yes or no**).	Randomized subjects will be stratified by the presence of cryptogenic cirrhosis to balance the number of subjects with cryptogenic cirrhosis between the two treatment arms (placebo vs. OCA).
Synopsis Analysis Populations Section 16.1 Analysis Populations	Insertion	**<u>Modified Intent-to-Treat (mITT) Population</u>** **The mITT Population will include all ITT subjects who dose titrate at Month 3 per protocol. Treatment assignment will be based on the randomized treatment.**	Additional analysis population added due to dose-titration design.
Synopsis Analysis Populations Section 16.1 Analysis Populations	• The Per Protocol (PP) Population will include all ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusions. Treatment assignment will be based on the randomized treatment.	• The Per Protocol (PP) Population will include all **m**ITT subjects who do not have any major protocol violations that potentially affect the efficacy conclusions. Treatment assignment will be based on the randomized treatment.	Clarification of PP Population due to addition of mITT population.
Synopsis Efficacy Analyses	Primary and key secondary efficacy hypothesis testing will be based on the ITT population. Exploratory analyses of	Primary and key secondary efficacy hypothesis testing will be based on the ITT population. Exploratory analyses of the primary endpoint	Modification due to addition of mITT population, modification of primary and key secondary

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	the primary endpoint will be conducted using PP population. The primary efficacy analysis will test the following hypotheses: • H_0: The percentage of subjects with fibrosis improvement by at least 1 stage using ~~Ishak~~ score from Baseline to Month 12 is equal between placebo and OCA ~~25 mg~~. • H_1: The percentage of subjects with fibrosis improvement by at least 1 stage using ~~Ishak~~ score from Baseline to Month 12 is different between placebo and OCA ~~25 mg~~. The type I error for the primary efficacy analysis will be controlled at ~~0.05.~~ For the comparison of the primary efficacy ~~endpoint~~, a Cochran–Mantel–Haenszel test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and ~~baseline fibrosis stage [Ishak 5 or 6]~~) will be used. Missing values will be considered a nonresponse. ~~Exploratory analyses of the primary endpoint will be conducted using PP population.~~ Key secondary efficacy endpoint~~s~~ ~~are~~: [redacted] • Percentage of subjects with fibrosis improvement by at least 2 stages using Ishak scoring criteria from Baseline to Month 12 ~~The hypothesis testing of key secondary endpoints will be conducted in a sequential closed testing gate-keeping procedure, provided the primary efficacy comparison is~~	will be conducted using the **mITT and** PP populations. The primary efficacy analysis will test the following hypotheses: • H_0: The percentage of subjects with fibrosis improvement by at least 1 stage using **NASH CRN** score from Baseline to Month 12 is equal between placebo and OCA. • H_1: The percentage of subjects with fibrosis improvement by at least 1 stage using **NASH CRN** score from Baseline to Month 12 is different between placebo and OCA. Key secondary efficacy endpoint is: • **Percentage of subjects with fibrosis improvement by at least 2 stages using Ishak scoring criteria from Baseline to Month 12** The type I error for the primary efficacy analysis will be controlled at **0.01**. **The hypothesis testing of primary and key secondary endpoints will be conducted in a sequential closed testing gate-keeping procedure**. For the comparison of the primary and **key secondary efficacy endpoints**, a Cochran–Mantel–Haenszel test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] **and cryptogenic cirrhosis [yes or no]**) will be used. Missing values will be considered a nonresponse. Additional secondary endpoints will be analyzed; however, statistical testing will be considered descriptive and exploratory only.	efficacy endpoints and randomization stratification factors. Modified type 1 error based on discussions with regulatory authorities.

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	~~statistically significant in favor of OCA. This procedure controls the study-wise type I error and is described below.~~ ~~First, placebo and OCA 25 mg will be compared with respect to the primary efficacy endpoint at Month 12. If the comparison of primary efficacy endpoint achieves statistical significance at the 2-sided 0.05 level in favor of OCA, then~~ ~~Placebo and OCA 25 mg will be compared with respect to improvement in liver histology by morphometric assessment of quantitative collagen (assessed as PCA) at Month 12. If the comparison achieves statistical significance at the 2-sided 0.05 level in favor of OCA, then~~ ~~Placebo and OCA 25 mg will be compared with respect to the percentage of subjects with fibrosis improvement by at least 1 stage using NASH CRN criteria from Baseline to Month 12, at 2-sided 0.05 level.~~ ~~If at any step defined above, the comparison is not statistically significant at the 2-sided 0.05 level, then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory.~~ Additional secondary endpoints will be analyzed; however, statistical testing will be considered descriptive and exploratory only. ~~Additional secondary analyses will be conducted using PP population.~~		
Synopsis Safety Analysis	Safety ~~data~~, including treatment-emergent AEs, vital signs, electrocardiograms (ECGs), and clinical laboratory results ~~will compare OCA 25 mg and placebo at Month 12.~~	Safety **evaluations will comprise** treatment-emergent AEs, **adjudicated CV events**, vital signs, electrocardiograms (ECGs), and clinical laboratory results.	Modified to include both double-blind and open label study periods.
Synopsis Sample Size Justification	A sample size of 180 subjects per group with an assumed ~~1~~0% discontinuation rate will provide ~~8~~0% power to demonstrate a statistically significant treatment difference between OCA and placebo group based on Chi-square test with 2-sided type I error at 0.0~~5~~ level, assuming a responder rate of ~~4~~3% and ~~2~~8% in the OCA and placebo groups,	A sample size of 180 subjects per group with an assumed **5**% discontinuation rate will provide **9**0% power to demonstrate a statistically significant treatment difference between OCA and placebo group based on Chi-square test with 2-sided type I error at 0.0**1** level, assuming a	Modified statistical assumptions due to emerging natural history data on NASH with cirrhosis and regulatory feedback.

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Section 16.2 Determination of Sample Size	respectively, based on data from literature and practical consideration.	responder rate of **2**3% and 8% in the OCA and placebo groups, respectively, based on data from literature, **observed effect size on fibrosis improvement in advanced fibrosis subjects in FLINT**, and practical consideration	
Section 5.4.1 Rationale for Study Design	Thus, Study 747-304 will evaluate efficacy and safety of OCA in subjects with NASH with cirrhosis (defined by a ~~Ishak score ≥5~~), with the exception of subjects with Child-Pugh (CP) score ≥7. The efficacy of OCA in this study will be evaluated based on histological improvement in fibrosis	Thus, Study 747-304 will evaluate efficacy and safety of OCA in subjects with NASH with cirrhosis (defined by a **NASH Clinical Research Network [CRN] score of 4)**, with the exception of subjects with Child-Pugh (CP) score ≥7. The efficacy of OCA in this study will be evaluated based on histological improvement in fibrosis.	Updated with NASH CRN criteria because these are considered more appropriate for the study population and the primary endpoint is based on NASH CRN criteria
Section 5.4.2 Rationale for Placebo Control Group	The use of a randomized placebo control group added to established standard of care provides the best scientific evidence of efficacy and safety.	The use of a randomized placebo control group added to established standard of care, **including lifestyle modification counseling**, provides the best scientific evidence of efficacy and safety.	Added clarification.
Section 5.4.3 Rationale for Obeticholic Acid Dose and Duration	Subjects will be randomized to receive OCA ~~25 mg~~ or placebo daily ~~during~~ the Double-Blind Phase. This dose was selected based clinical experience in completed Phase 2 studies in subjects with NAFLD (747-203) and NASH (FLINT) as well as a clinical pharmacology study in subjects with hepatic impairment (Study 747-103).	Subjects will be randomized to receive OCA **10 mg** or placebo daily **for the first 3 months then titrate to OCA 25 mg or placebo daily for the duration of** the Double-Blind Phase. This dose **titration was selected based on the known mechanism of FXR and** clinical experience in completed Phase 2 studies in subjects with NAFLD (747-203) and NASH (FLINT) as well as a clinical pharmacology study in subjects with hepatic impairment (Study 747-103). **FXR is a nuclear receptor that senses bile acids and regulates their intracellular levels in hepatocytes. FXR activation leads to the reduction of intracellular bile acid levels by increasing the export of bile acids out of cells,**	Updated dose rationale to incorporate 10 mg dose. Incorporated FXR activation as key rationale for selection of titration dose regimen.

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		thereby decreasing bile acid uptake and bile acid synthesis. After 12 weeks of dosing OCA, FXR activation has been shown to reduce systemic bile acid levels while maintaining relatively low OCA levels in the total bile acid pool (<2%).	
Section 5.4.3 Rationale for Obeticholic Acid Dose and Duration	The dedicated hepatic impairment study (747-103) using OCA 10 mg has shown only 10% increase in the systemic concentrations of total OCA in subjects with CP Class A compared to healthy subjects. ~~Because a linear relationship from doses of OCA 5 mg up to OCA 100 mg has been demonstrated (Studies 747-102, 747-103, 747-105, 747-112, and 747-115), it is expected that similar systemic exposures of OCA 25 mg will be observed in subjects with CP Class A compared to noncirrhotic subjects.~~ Therefore, the OCA ~~25~~ mg dose ~~is considered appropriate for evaluation of safety and efficacy of OCA in all eligible subjects at study entry~~. Guidelines for subjects who progress beyond CP Class A are provided in Section 7.5. ~~S~~tudy duration was determined based on findings in prior NASH studies ranging from 6 months to 72 weeks	The dedicated hepatic impairment study (747-103) using OCA 10 mg has shown only 10% increase in the systemic concentrations of total OCA in subjects with CP Class A compared to **that of** healthy subjects. Therefore, the **dose of** OCA **10** mg **will be administered for 3 months to support the lowering of bile acid levels in CP Class A subjects**. **After 3 months, titration of OCA 25 mg administration is introduced to provide clinically proven beneficial doses**. Guidelines for subjects who progress beyond CP Class A are provided in Section 7.6. **The duration of the 12-week titration is based upon results seen in the prior PBC program which effectively demonstrated titration for biologically altering the FXR signaling pathways thus inducing bile acid levels**. **Overall s**tudy duration was determined based on findings in prior NASH studies ranging from 6 months to 72 weeks.	To incorporate the titration dose justification based upon FXR MOA and prior study experience.
Section 5.5 Summary of Known Potential Risks with	~~An increase in liver enzymes and hepatic AEs, including jaundice, were observed in subjects with liver disease at OCA doses between 10 mg and 50 mg and in healthy subjects who were treated at doses ≥100 mg in Phase 1, multiple-dose studies.~~	**Consistent with the dose-limiting hepatic toxicities observed in the non-clinical studies, dose-related but reversible and asymptomatic increases in ALT and AST were observed in healthy volunteers treated with multiple**	Safety language updated

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Investigational Product		**doses of OCA starting at the 100 mg dose (Study 747-102).** **In patients with chronic liver disease such as PBC, hepatobiliary findings including increased transaminases and bilirubin and signs or symptoms of hepatic decompensation such as development of jaundice were observed. In addition, cholecystitis, including acute cholecystitis, was reported in association with treatment with OCA.**	
Section 6.1 Primary Objective	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage using ~~Ishak s~~coring ~~criteria~~ from Baseline to Month 12	• Histological improvement in fibrosis by assessing the percentage of subjects with improvement in fibrosis by at least 1 stage using **the NASH CRN** scoring **system** from Baseline to Month 12	Updated with NASH CRN criteria because the primary endpoint using the NASH CRN criteria is considered more appropriate for this population.
Section 7.1.2 Schedule of Study Procedures: Double-Blind Phase Table 1	Insertion	**Mth 2, Mth 4, Mth 5 procedures**	Additional study visits for safety monitoring.
Section 7.1.2 Schedule of Study Procedures: Double-Blind Phase Table 1	Insertion Change in intervals for assessment of HbA1c	**Microbiome/Metabalome Stool Sample Analysis (All US Subjects) assessments at Day 1, Month 1, Month 3, Month 6, Month 12, ET ELF at Month 3, Month 9** **TE, Liver Multiscan, and MRE et Month 3, Month 9** **Metabolic Parameter: HbA1c. Assessments at Screening Visit 1, Day 1, Months 3, 6, 9 and 12.**	Examination of microbiota and their metabolites in a well-defined NASH population, as proposed in this study, could provide additional insight into NASH pathogenicity. Since OCA has been shown to impact dysbiosis in animal models,

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		Other Metabolic Parameters split into separate row.	its effect in NASH subjects will be evaluated via examination of fecal gut microbiome, fecal metabolomes, and fecal bile acid composition.
Section 7.1.2 Schedule of Study Procedures: Double-Blind Phase Table 1	[a] ~~Not required for subjects who have had a biopsy ≤6 months prior to randomization (Day 1) and can provide unstained slides.~~	[a] The 2 Screening Visits must occur at least 4 weeks apart to confirm pretreatment serum chemistry levels, including ALT and AST.	Footnotes updated to align with updated text and procedures.
Section 7.1.2 Schedule of Study Procedures: Double-Blind Phase Table 1	[m] On-study liver biopsies should be performed after the hepatobiliary ultrasound for HCC screening. [n] Optional procedure. If a biopsy was obtained within ~~6~~ months, subjects do not need to undergo this procedure [q] At the Month 1 and Month 12/EOT/EOS visit, investigational product administered will be from the bottle dispensed at the previous visit.	[m] On-study liver biopsies should be performed after the hepatobiliary ultrasound for HCC screening. **Liver biopsy procedure at Screening Visit 2 is not required for subjects who have had a biopsy ≤12 months prior to randomization (Day 1) and can provide unstained slides**. [n] Optional procedure. If a biopsy was obtained within **12** months, subjects do not need to undergo this procedure. [q] At the Month 1, **2, 4, 5,** and Month 12/EOT/EOS visit, investigational product administered will be from the bottle dispensed at the previous visit. [s] **Other metabolic parameters include fasting plasma glucose, insulin, C-peptide, and HOMA-IR.**	Footnotes updated to align with updated text and procedures.
Section 7.1.2 Schedule of Study Procedures: Double-Blind Phase Table 1	Insertion	**[r] In the event either of the 2 ALT/AST assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample will be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may

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			result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations. Additional safety and tolerability considerations including dose titration is required in this vulnerable population with decreased hepatic reserve.
Section 7.1.2 Schedule of Study Procedures: OLE Phase Table 2	Insertion Change in intervals for assessment of HbA1c	**Mth 2, Mth, 3, Mth 4, Mth 5 procedures** **Metabolic Parameter: HbA1c. Assessments at Day 1, Months 3, 6, 9, 12, 15, 18, 21, 24/EOT/EOS, and ET.** **Other Metabolic Parameters** split into separate row.	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations. Additional safety and tolerability considerations including dose titration is required in this vulnerable population with decreased hepatic reserve.

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Section 7.1.2 Schedule of Study Procedures: OLE Phase Table 2	[g] Subjects randomized to placebo during the Double-Blind Phase will receive OCA 25 mg in the OLE. Subjects randomized to OCA during the Double-Blind Phase will continue the treatment they were assigned. [j] At the Month 1 and/or Month 24/EOT/EOS visit, investigational product dispensed/administered will be from the bottle issued at the previous visit.	[g] Subjects randomized to placebo during the Double-Blind Phase will receive **OCA 10 mg for 3 months followed** by OCA 25 mg in the OLE, **unless there are safety concerns**. Subjects randomized to OCA during the Double-Blind Phase will continue the treatment they were assigned. [j] At the Month 1, **2, 4, 5**, and/or Month 24/EOT/EOS visit, investigational product dispensed/administered will be from the bottle issued at the previous visit.	Titration schedule followed in the double-blind phase, continued in the open-label phase of the study. Clarification on dispensing of investigational product.
7.3 ~~Treatment Assignment~~ **Planned Dosing Regimen**	Subjects will be randomly assigned in a 1:1 ratio to receive placebo or OCA ~~25 mg~~.	Subjects will be randomly assigned in a 1:1 ratio to receive placebo or OCA. **Following assessments of liver chemistry and safety at Month 1 and Month 2, a dose titration to 25 mg or matching placebo will be implemented at Month 3, unless there are safety and tolerability concerns.**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations. Additional safety and tolerability considerations including dose titration is required in this vulnerable population with decreased hepatic reserve.
7.4 Management of	~~For~~ a subject who ~~reaches a~~ CP score ≥7 ~~(CP Class B or C), an adjustment to the dose frequency will be implemented~~	**A subject who progresses to CP Class B or C cirrhosis (**CP score ≥7**) will discontinue**	Cirrhotic patients have diminished hepatocellular function, lesser ability to

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Disease Progression	(see Section 7.5~~) and serial PK samples will be collected (see Section 13.1)~~. Monitoring of disease progression using CP score and MELD will be continued throughout the study (Schedule of Study Procedures Table 1).	**investigational product** (Section), and the subject should be followed for the duration of the study. **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.** Monitoring of disease progression using CP score and MELD will be continued throughout the study (Schedule of Study Procedures Table 1). **In addition, subjects should be re-assessed within a month for disease progression. At a minimum, a physical exam, general biochemistry, serum electrolytes, and assessment of CP and MELD scores should be conducted. Further monitoring outside of regular scheduled visits should be based on the Investigator's assessment of the subject's clinical status.**	recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, liver disease progression defined by CP score will require study drug discontinuations.
Section 7.5 Dosage Adjustment	-	Deletion	CP language was modified
Section 7.5 Dosage Adjustment	~~Dosages for investigational product should be maintained constant during the study.~~ However, dose frequency may be modified for the management of pruritus or other safety findings as described in Section 15.1.5.1. ~~If during the study, a subject progresses to CP score ≥7 (CP Class B or C), the Investigator should reduce the dose frequency of the randomized investigational product to every other day administration. In addition, subjects~~	**With an exception of the planned dose titration at Month 3, dosages for investigational product should be maintained constant during the study.** However, dose frequency may be modified for the management of pruritus or other safety findings as described in Section 15.1.4.1.	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. Additional safety and tolerability considerations including dose reduction may be

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	~~should be re-assessed within a month for disease progression. At a minimum, a physical exam, liver biochemistry, prothrombin time (PT)/INR, serum electrolytes, and assessment of CP and MELD scores should be conducted. Further monitoring outside of regular scheduled visits should be based on the investigator's assessment of the subject's clinical status~~	**In the event of tolerability issues such as pruritus, the dosing frequency may be decreased at the discretion of the Investigator.** **If at any point, safety concerns are noted based on review of liver biochemistry and adverse events, down titration to 10 mg daily may be considered in consultation with the medical monitor.**	required in this population with decreased hepatic reserve.
Section 8.1 Subject Population	This study will be conducted at approximately ~~75 to 100~~ international study sites with experience in treating patients with compensated cirrhosis due to NASH	This study will be conducted at approximately **150** international study sites with experience in treating patients with compensated cirrhosis due to NASH	Additional sites will be utilized to ensure enrollment of subjects.
Section **8.2.1.1 Progression to CP score ≥7**	Insertion	**If a subject develops a CP score ≥7, liver-related assessments used in CP score calculation should be confirmed within 48 to 72 hours and captured in the EDC. If CP score is confirmed, a mandatory discontinuation of investigational product is required. 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.**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, liver disease progression defined by CP score will require study drug discontinuations. Following FDA guidance, discontinuation criteria were updated for subjects

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			who progress to CP score ≥7
~~Section 8.2.1.2 Severe Drug Induced Liver Injury~~	~~Subjects who develop severe drug-induced liver injury, which is considered to be causally related to the investigational product, should be discontinued from investigational product and should not be rechallenged. Using the investigator's clinical judgement, laboratory measures may be repeated for clinical confirmation. Subjects who discontinue investigational product are expected to be followed though to study closure (or at the discretion of the Sponsor).~~ ~~Severe drug-induced liver injury is described in detail in Appendix B. Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued. Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.~~ ~~Severe drug-induced liver injury that is not considered related to investigational product must be discussed with the Sponsor before investigational product is reinitiated. Follow-up procedures for subjects resuming treatment, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject is to be allowed to continue treatment. Subjects should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time.~~	**Deletion**	Language on drug-induced liver injury was combined and streamlined in Section 8.2.2.2.

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Section 8.2.2.2 Suspected ~~Mild or Moderate~~ Drug-Induced Liver Injury	~~Because transient fluctuations of ALT or AST are common, and progression to severe drug-induced liver injury or acute liver failure is uncommon, automatic discontinuation of investigational product with an elevation of ALT or AST that is >3x ULN/baseline/nadir or total bilirubin >2x ULN/baseline/nadir, as described in Appendix B, may be unnecessary. If a subject develops signs of a mild or moderate event of drug-induced liver injury, regardless of causality, investigational product should be interrupted until the event has resolved or returned to baseline but the subject should continue with the study visit schedule.~~ ~~The subject may restart treatment after resolution of the event or return to baseline.~~ Follow-up procedures, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of re-treatment and may be conducted at a local clinic if the subject is unable to return to the site. Results must be reported immediately to the site so the Investigator can determine if the subject ~~will~~ be allowed to continue treatment.	**Cirrhotic patients have diminished liver reserve and lesser ability to recover, and these could make the consequences of a drug-induced injury worse. Their transaminase, especially ALT, levels may be normal or only slightly elevated, due to their lower hepatocellular reserve, even in advanced cases. For this reason, relatively lower level of transaminase elevations can indicate severe drug-induced liver injury and may require investigational product discontinuations. Subjects who discontinue investigational product are expected to be followed though to study closure (or at the discretion of the Sponsor) and should be encouraged to continue study visits despite stopping investigational product for continued study data collection but may withdraw consent at any time.** **Natural progression of the underlying condition and other causal factors such as a common bile duct stone or development of other concurrent liver disease should be considered before the investigational product is permanently discontinued. Subjects who discontinue due to significant drug-induced liver injury must be followed until the AE has resolved, stabilized, or is not of clinical concern.** • **Investigational product must be interrupted in subjects if the following conditions develop: Baseline values were <2x ULN, and ALT or AST increases to >5x baseline measurement (BLM).**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, liver disease progression defined by CP score will require study drug discontinuations.

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		• **Baseline values were ≥2x ULN but <5x ULN, and ALT or AST increases to >3x BLM** • **Baseline values were ≥5x ULN, and ALT or AST increases to >2x BLM** • **ALT or AST increase >2x BLM AND the increase is accompanied by a concomitant total bilirubin increase to >2x BLM OR the INR concomitantly increases by >0.2.** **Investigational product will also be interrupted in presence of signs and symptom(s) such as rash, eosinophilia, nausea, vomiting, or right upper quadrant pain, anorexia and fatigue irrespective of the transaminase level, if the bilirubin is elevated above 2x BLM. A potential drug-induced liver injury work-up for competing etiologies must be performed, and a complete liver profile including prothrombin time (PT)/INR must be repeated within 48-72 hours. Study medication can be restarted only if an alternative etiology is definitively identified and liver tests have returned to baseline.** Follow-up procedures, including laboratory evaluations and physical examinations, must be performed after a maximum of 2 weeks of retreatment and may be conducted at a local clinic if the subject is unable to return to the site. **In this case,** results **as well as normal laboratory ranges,** must be reported immediately to the site**, and included in the case reports,** so the Investigator can determine	

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		if the subject **is to** be allowed to continue treatment.	
Section 9.1 Investigational Product Treatment Regimen	Two treatment groups will be evaluated: • Placebo • OCA 25 mg Each dose will be made up of 1 tablet ~~(ie, one placebo tablet or one OCA 25 mg tablet)~~.	Two treatment groups will be evaluated: • Placebo • OCA **(10 mg and** 25 mg**)** Each dose will be made up of 1 tablet.	Inclusion of 10 mg dose due to study design changes.
Section 9.1.1 OLE Phase	Investigational product during the OLE Phase will be provided as open label OCA tablets ~~at strength of 25 mg~~.	Investigational product during the OLE Phase will be provided as open-label OCA tablets.	Placebo subjects will be receiving 3 months of OCA 10 mg before uptitrating to OCA 25 mg.
Section 9.4.1 Methods of Assigning Subjects to Treatment Groups	This study will be conducted in a double-blind, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1 ratio to placebo or OCA ~~25 mg~~ based on a predefined randomization code (generated by Sponsor or designee) using an IWRS. Randomization of subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no) and ~~Ishak cirrhosis score 5 or 6.~~ All subjects who enroll into the OLE will receive OCA ~~25 mg~~.	This study will be conducted in a double-blind, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1 ratio to placebo or OCA based on a predefined randomization code (generated by Sponsor or designee) using an IWRS. **Subjects randomized to OCA will initiate investigational product of OCA 10 mg for 3 months prior to uptitrating to OCA 25 mg. Uptitration will be based on safety and tolerability assessments completed at Month 1, Month 2, and Month 3.** Randomization of subjects will be stratified by the presence of type 2 diabetes at enrollment (yes or no) and **cryptogenic cirrhosis (yes or no).** All subjects who enroll into the OLE will receive OCA. All subjects who enroll into the OLE will receive OCA. **Subjects randomized to placebo in the double blind period will initiate investigational product of OCA 10 mg for the**	Inclusion of 10 mg dose due to study design changes.

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		first 3 months of the OLE prior to uptitrating to OCA 25 mg. Uptitration will be based on safety and tolerability assessments completed at Month 1, Month 2, and Month 3. Subjects will continue the same dosing regimen they received at the end of the Double-Blind Phase.	
Section 9.4.1 Methods of Assigning Subjects to Treatment Groups	Insertion	**To maintain blinding after subjects complete the Double-Blind Phase and enter the OLE, all placebo, OCA 10 mg, and OCA 25 mg tablets and bottles will be identical. Once all subjects have titrated to the OCA 25 mg dose in the OLE, subjects may receive investigational product with an open label identifying the product as OCA 25 mg.**	Information on how blinding will be maintained as subjects enter the OLE.
Section 9.7.3 Screening Visit Procedures	Insertion	**Two Screening Visit assessments must be performed to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be rescreened after 2 months have elapsed from the date of their most recent screening visit procedure; however, all Screening procedures (including obtaining informed consent) should be repeated and a new three-digit Screening number assigned.** **The 2 Screening visits must occur at least 4 weeks apart to confirm pretreatment serum chemistry levels, including ALT and AST.** • **Screening Visit 1 will occur 8 weeks prior to Day 1;** • **Screening Visit 2 will occur 4 weeks ± 2 days prior to Day 1, depending on**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations. Additional study visits will allow a closer safety monitoring to detect disease progression signals.

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		the date that the first serum chemistry sample was collected. **If either the 2 ALT or 2 AST assessments collected at Screening Visit 1 and Screening Visit 2 differ by ≥30%, a third sample must be collected at an unscheduled visit as a confirmatory sample to include in the mean result(s) that will be used to determine eligibility.**	
Section 9.7.3.1 Screening Visit 1	The Screening Visit assessments must be performed within ≤8 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria • Assess availability of liver biopsy samples obtained ≤6 months prior to Day 1, for which unstained slides can be prepared and submitted for central review • Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted). Fasting is ~~not~~ required before Screening Visit 2.	The Screening Visit assessments must be performed within ≤8 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria • Assess availability of liver biopsy samples obtained ≤12 months prior to Day 1, for which unstained slides can be prepared and submitted for central review • Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted). Fasting is required before Screening Visit 2.	To allow for AST and ALT assessments to be conducted twice.
Section 9.7.3.2 Screening Visit 2	Screening Visit 2 procedures ~~for all subjects without a recent liver biopsy with unstained slides~~ must be performed within ≤~~8~~ weeks prior to Day 1 and are as follows:	Screening Visit 2 procedures must be performed within ≤**4** weeks ± **2 days** prior to Day 1 and are as follows:	Updated to require all subjects to follow updated screening procedures.
Section 9.7.3.2 Screening Visit 2	Insertion	• **Verify that the subject has fasted for at least 8 hours**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure

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		– **Record fasting status in the source and eCRF** • **If the subject reports having eaten within 8 hours, document accordingly in the source and eCRF and remind the subject that fasting is required before all study visits** • **Medical History** • **Obtain urine sample for urinalysis** • **Obtain blood samples for:** o **Serum chemistry, hematology, and coagulation** • **Calculations will be performed by the Sponsor or designee for:** o **MELD Score** o **CP Score/Class** • **Perform a urine-based beta human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential**	relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations.
Section 9.7.4 Day 1 Procedures **9.7.5 Month 1 Procedures** **9.7.7 Month 3 and Month 9 Procedures**	Insertion	• **Obtain stool sample (collected at home) for microbiome/metabolome analysis (US subjects only)**	Examination of microbiota and their metabolites in a well-defined NASH population, as proposed in this study, could provide additional insight into NASH pathogenicity and may also potentially serve as a non-invasive marker of fibrosis. Since OCA has

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9.7.7 Month 6 Procedures **9.7.11 Month 12/EOT/EOS Procedures** **9.7.13 Early Termination Procedures**			been shown to normalize dysbiosis in animal models, its effect in NASH subjects will be evaluated via examination of fecal gut microbiome, fecal metabolomics, and fecal bile acid composition.
Section 9.7.6 Month 2 Procedures **Section 9.7.8 Month 4 Procedures** **Section 9.7.9 Month 5 Procedures**	Insertion	**Section 9.7.6 Month 2 Procedures** **Section 9.7.8 Month 4 Procedures** **Section 9.7.9 Month 5 Procedures**	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations. Additional study visits will allow a closer safety monitoring to detect disease progression signals.
Section 9.7.7 Month 3 and Month 9 Procedures	Insertion	• **Month 3: Obtain stool sample (collected at home) for microbiome/metabolome analysis (US subjects only)** • **Noninvasive panel of liver fibrosis (ELF, FibroMax, and FibroMeter)**	Examination of microbiota and their metabolites in biopsy-confirmed cirrhotic subjects, as proposed in this study, could provide additional insight into NASH pathogenicity and

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
		• **Month 3: Noninvasive radiological liver fibrosis measurements (TE, Liver*MultiScan*, and MRE; conducted at sites where device is available) if not conducted during Screening. Whichever modality/ies used at baseline must be collected consistently at each visit.**	may also potentially serve as a non-invasive marker of fibrosis. Since OCA has been shown to impact dysbiosis in animal models, its effect in cirrhotic subjects will be evaluated via examination of fecal gut microbiome, fecal metabolomics, and fecal bile acid composition
Section 9.7.13. Month **2,** 3, **5**, 9, 15, and 21 OLE	Section 9.7.13. Month 3, 9, 15, and 21 OLE • Calculations will be performed by the Sponsor or designee for: – Noninvasive panel of liver fibrosis (ELF, FibroMax, and FibroMeter)	Section 9.7.13. Month **2,** 3, **5**, 9, 15, and 21 OLE – **Month 2, 5: Trough PK (All Subjects)** – **Month 2, 5: PD Blood Samples (All Subjects)** • Calculations will be performed by the Sponsor or designee for: – **Month 3 OLE:** Noninvasive panel of liver fibrosis (ELF, FibroMax, and FibroMeter)	Cirrhotic patients have diminished hepatocellular function, lesser ability to recover, and may progress into end stage liver failure relatively faster. As mentioned above this may result in increased serum concentrations of IP and since optimal dosing for subjects with hepatic impairment has not yet been determined, these subjects will require study drug discontinuations. Additional study visits will allow a closer safety monitoring to detect disease progression signals.
Section 9.7.14. Month 4 OLE	Insertion	**Section 9.7.14. Month 4 OLE**	Additional study visits will allow a closer safety monitoring to detect disease progression signals.

<table>
<tr><th>Section</th><th>Original Text (Version 1.0)</th><th>Revised Text (Version 2.0)</th><th>Key Change
Reasons/Justification for Change</th></tr>
<tr><td>Section 10.1 Investigational Product</td><td>Investigational Product will be supplied as white, round, film-coated tablets containing~~,~~ OCA 25 mg, or placebo.</td><td>Investigational Product will be supplied as white, round, film-coated tablets containing OCA 10 mg, OCA 25 mg, or placebo.</td><td>Inclusion of 10 mg dose due to study design changes.</td></tr>
<tr><td>Section 12.1. Liver Biopsy</td><td>Given that historical biopsies are to be obtained no more than ~~6~~ months before Day 1 …</td><td>Given that historical biopsies are to be obtained no more than 12 months before Day 1 …</td><td>The window of historic biopsy changed from 6 months to 12 months before Day 1 because the NASH CRN fibrosis score of a cirrhotic patient is unlikely to improve to a lower fibrosis score within 12 months, if all other entry criteria are met.</td></tr>
<tr><td>Section 12.1. Liver Biopsy</td><td>~~Biopsies should be at least 2 cm in length.~~</td><td>Deletion</td><td>Specifics will be provided in the manual.</td></tr>
<tr><td>Section 12.1.1 Central Reading of Liver Histology</td><td>Histological presence of NASH with a~~n Ishak fibrosis score ≥5~~ or cryptogenic cirrhosis assumed to be due to NASH must be confirmed for study eligibility. For each biopsy, fibrosis will be graded in accordance with ~~Ishak scoring system~~ (Table 3) ~~(Ishak 1995)~~.

~~Table 11:~~ ~~Ishak Scoring System~~ for Determining Eligibility and Primary Histological Endpoint Assessment

<table><tr><th colspan="2">~~Modified Staging: Architectural Changes, Fibrosis, and Cirrhosis~~</th></tr><tr><td>~~Change~~</td><td>~~Score~~</td></tr><tr><td>~~No fibrosis~~</td><td>~~0~~</td></tr></table></td><td>Histological presence of NASH with a fibrosis score of 4 based on the NASH CRN or cryptogenic cirrhosis with metabolic factors assumed to be due to NASH must be confirmed for study eligibility. For each biopsy, fibrosis will be graded in accordance with the NASH CRN scoring system (Table 3) (Kleiner 2005).

Table 3: NASH CRN Scoring System for Determining Eligibility and Primary Histological Endpoint Assessment

<table><tr><th colspan="2">NAFLD Activity Score (NAS)</th></tr><tr><td>Parameter</td><td>Scoring Criteria</td></tr><tr><td>Steatosis</td><td>0 = <5%</td></tr></table></td><td>Updated with NASH CRN criteria because these are considered more appropriate for the study population and the primary endpoint is based on NASH CRN criteria.</td></tr>
</table>

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
	~~Fibrous expansion of some portal areas, with or without short fibrous septa~~ ~~1~~ ~~Fibrous expansion of most portal areas, with or without short fibrous septa~~ ~~2~~ ~~Fibrous expansion of most portal areas with occasional portal to portal bridging~~ ~~3~~ ~~Fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central~~ ~~4~~ ~~Marked bridging (portal to portal and/or portal to central) with occasional nodules (incomplete cirrhosis)~~ ~~5~~ ~~Cirrhosis, probably or definite~~ ~~6~~ ~~Adapted from Ishak 1995.~~ In addition to the primary scoring of ~~Ishak~~, biopsy samples will also be scored based on the ~~NASH CRN~~ criteria (Kleiner 2005), Laennec staging (Wang 2015), and SAF scoring (Bedossa 2014), and for quantitative collagen ~~and percent fat~~.	**1 = 5% - 33%** **2 = >33% - 66%** **3 = >66%** **Lobular Inflammation** **0 = No Foci** **1 = <2 Foci per 200 × field** **2 = 2-4 Foci per 200 × field** **3 = > 4 Foci per 200 × field** **Ballooning** **0 = None** **1 = Few balloon cells** **2 = Many cells / prominent ballooning** In addition to the primary scoring of **NASH CRN,** biopsy samples will also be scored based on the **modified Ishak** criteria (Ishak 1995), Laennec staging (Wang 2015), and SAF scoring (Bedossa 2014), and for quantitative collagen.	
Section 12.1.1 Central Reading of Liver Histology	In addition to the primary scoring ~~of Ishak~~, biopsy samples will also be scored based on the ~~NASH CRN~~ criteria (~~Kleiner 2005~~), Laennec staging (Wang 2015), and SAF	In addition to the primary scoring **using NASH CRN**, biopsy samples will also be scored based on the Ishak criteria (Ishak 1995), Laennec	NASH CRN used here because considered more appropriate for the study population and the primary

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
	scoring (Bedossa 2014), and for quantitative collagen ~~and percent fat~~.	staging (Wang 2015), and SAF scoring (Bedossa 2014), and for quantitative collagen.	endpoint is based on NASH CRN criteria.
Section 13.1 Pharmacokinetic Blood Sampling	Subjects may opt to provide blood samples for serial PK assessments. ~~Trough PK blood samples will be obtained from all subjects.~~	Subjects may opt to provide blood samples for serial PK assessments. **Serial blood samples will be used to characterize the PK at steady-state for a cohort of subjects at both OCA 10 mg and (when titrated) 25 mg doses. An assessment of steady-state exposures (on an aggregate level) will be performed by an internal Intercept clinical pharmacologist/ pharmacometrician who is discrete from the study team. These results may be made available to the DMC as appropriate (see Section 16.13).**	To best assess exposure and safety data across the duration of the trial, an unblinded pharmacometrician outside of the study team will analyze data and provide results to the DMC.
Section 13.1 Pharmacokinetic Blood Sampling	No other food or drink (water is permitted) will be allowed until after the 6-hour sample collection.	No other food or drink (water is permitted) will be allowed until after the 6-hour sample collection. **Trough PK blood samples will be obtained from all subjects.**	Because trough PK samples must be taken from subjects who have fasted, a clarifying statement for collection of PK samples after the 6-hour fast was added.
Section 13.1 Pharmacokinetic Blood Sampling	During the Double-Blind Phase: • Serial PK samples will be obtained at Month 1 and Month 12 from subjects who agree to participate in the assessment. • Trough samples will be obtained from all subjects prior to dose administration from all subjects at Months 1, 3, 6, 9, 12, and ET. During the OLE Phase:	During the Double-Blind Phase: • Serial PK samples will be obtained at Month 1, **Month 4**, and Month 12 from subjects who agree to participate in the assessment. • Trough samples will be obtained from all subjects prior to dose administration from all subjects at Months 1, **2,** 3, **4, 5**, 6, 9, 12, and ET.	Because the titration schedule necessitates the need for steady state PK data at both 10 and 25 mg doses, an additional assessment at Month 4 was added. Because of the added visit days to the schedule, additional PK samples will

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
	• Subjects who agree to participate in the Serial PK assessments will have samples obtained at Month 1 ~~OLE~~ and Month 24 OLE. • Trough PK samples will be obtained from all subjects prior to dose administration on Months 1, 6, 12, 18, 24 OLE, and ET.	During the OLE Phase: • Subjects who agree to participate in the Serial PK assessments will have samples obtained at Month 1**, Month 4,** and Month 24 OLE. • Trough PK samples will be obtained from all subjects prior to dose administration on Months 1**, 2, 3, 4, 5**, 6, 12, 18, 24 OLE, and ET.	be collected to measure drug exposure. To align serial PK sampling from the double-blind phase with the OLE Phase, an additional 4 month assessment was added.
Section 14.3 Microbiome/Metabolome Analysis	Insertion	**Stool specimens collected for microbiome/metabolome analyses will be collected from all subjects at US sites. Specimens will undergo microbiota 16S ribosomal RNA gene analysis, genome testing, fecal metabolomics, fecal bile acid analysis, and other appropriate assays to determine if and how OCA influences the composition and activity of the resident microbiota in the gastrointestinal tract. Subjects will be provided kits and instructions for collection of stool specimens at home, as appropriate.** **Microbiome/metabolome analyses will be assessed in subjects according to the schedule presented in Schedule of Study Procedures Table 1 (Double-Blind Phase).**	Examination of microbiota and their metabolites in biopsy-confirmed cirrhotic subjects, as proposed in this study, could provide additional insight into NASH pathogenicity and may also potentially serve as a non-invasive marker of fibrosis. Since OCA has been shown to impact dysbiosis in animal models, its effect in cirrhotic subjects will be evaluated via examination of fecal gut microbiome, fecal metabolomics, and fecal bile acid composition.
Section 14.4.2 Exploratory Biomarkers	[redacted]	[redacted]	Added language to allow for additional biomarkers not yet identified.

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	[redacted]		
Section 15.1.3 Relationship to Study Procedures Table 7	A reaction that follows a reasonable temporal sequence from the liver biopsy; that follows a known or expected response pattern to the ~~liver biopsy~~.	A reaction that follows a reasonable temporal sequence from the **required procedure (eg,** liver biopsy**)**; that follows a known or expected response pattern to the **required study procedure**.	Updated to indicate that this applies to any study procedure.
Section 15.1.4.1 Severity of Pruritus (as an Adverse Event)	~~For subjects with mild or moderate pruritus, consider dose frequency adjustment (OLE only), dosing frequency and/or temporary dosing interruption~~	**Less frequent dosing of investigational product (eg, on alternate days) may be tried, after which subjects may return to their original daily dose as soon as tolerated.**	Language updated to match safety language in other protocols.
Section 15.1.9 Notification of Post-Study SAEs	Insertion	**All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours by following the instructions provided in Section 15.1.5.** **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 (ie, within 24 hours) by following the instructions provided in Section 15.1.5.**	Updated safety reporting including with additional instructions.
Section 15.2.7 Laboratory Assessments	CHI3L1 and P3NP	CHI3L1, P3NP, and emerging biomarkers for NASH diagnosis and/or pathophysiology	Additional biomarkers for NASH will be assessed

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Table 10			
Section 15.2.7 Laboratory Assessments Table 10	Microbiome/Metabolome Analysis (Double-Blind only)	Microbiota 16S ribosomal RNA gene analysis, genome testing, fecal metabolomics, fecal bile acid analysis, and other appropriate assays to determine if and how OCA influences the composition and activity of the resident microbiota in the gastrointestinal tract	Microbiome will be assessed in this population
Section 16.3 Primary Efficacy Analysis	The primary efficacy analysis will be conducted using the ITT population and test the following hypotheses: • H_0: The percentage of subjects with fibrosis improvement by at least 1 stage using ~~Ishak~~ score from Baseline to Month 12 is equal between placebo and OCA 25 mg. • H_1: The percentage of subjects with fibrosis improvement by at least 1 stage using ~~Ishak~~ score from Baseline to Month 12 is different between placebo and OCA 25 mg. The type I error for primary efficacy analysis will be controlled at 0.0~~5~~. For the comparison of the primary efficacy endpoint, a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and b~~aseline fibrosis stage [Ishak 5 or 6])~~ will be used. Missing values will be considered a nonresponse. Exploratory analyses of the primary endpoint will be conducted using PP population.	The primary efficacy analysis will be conducted using the ITT population and test the following hypotheses: • H_0: The percentage of subjects with fibrosis improvement by at least 1 stage using **NASH CRN** score from Baseline to Month 12 is equal between placebo and OCA. • H_1: The percentage of subjects with fibrosis improvement by at least 1 stage using **NASH CRN** score from Baseline to Month 12 is different between placebo and OCA. The type I error for primary efficacy analysis will be controlled at 0.0**1**. For the comparison of the primary efficacy endpoint, a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] **and cryptogenic cirrhosis [yes/no])** will be used. Missing values will be considered a nonresponse.	Modification due to addition of mITT population, modification of primary and key secondary efficacy endpoints and randomization stratification factors. Modified type 1 error based on discussions with regulatory authorities.

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		Exploratory analyses of the primary endpoint will be conducted using the **mITT** and PP populations.	
Section 16.4 Key Secondary Efficacy Analyses	Key secondary efficacy endpoint~~s~~ are: [redacted] • Percentage of subjects with fibrosis improvement by at least ~~1~~ stage using ~~NASH CRN~~ criteria from Baseline to Month 12 [redacted] be conducted in a sequential closed testing gate-keeping procedure, provided the primary efficacy comparison is statistically significant in favor of OCA. If the primary efficacy comparison is not statistically significant, then the comparison of key secondary efficacy endpoint~~s~~ will be considered descriptive and exploratory. ~~This procedure controls the study-wise type I error and is described below~~. ~~First, placebo and OCA 25 mg will be compared with respect to the primary efficacy endpoint at Month 12. If the comparison of primary efficacy endpoint~~	Key secondary efficacy endpoint is: • Percentage of subjects with fibrosis improvement by at least **2** stages using **Ishak scoring** criteria from Baseline to Month 12 The percentage of subjects with fibrosis improvement by at least 2 stages using **Ishak scoring** criteria will be analyzed **similarly to the primary endpoint**. The hypothesis testing of **the** key secondary endpoint will be conducted in a sequential closed testing gate-keeping procedure, provided the primary efficacy comparison is statistically significant in favor of OCA. If the primary efficacy comparison is not statistically significant, then the comparison of key secondary efficacy endpoint will be considered descriptive and exploratory.	Modified key secondary efficacy endpoint.

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	~~achieves statistical significance at the 2-sided 0.05 level in favor of OCA, then~~ ~~Placebo and OCA 25 mg will be compared with respect to improvement in liver histology by morphometric assessment of quantitative collagen (assessed as [redacted]) at Month 12. If the comparison achieves statistical significance at the 2-sided 0.05 level in favor of OCA, then~~ ~~Placebo and OCA 25 mg will be compared with respect to the percentage of subjects with fibrosis improvement of at least 1 stage using NASH CRN criteria from Baseline to Month 12 at the 2-sided 0.05 level.~~ ~~If at any step defined above, the comparison is not statistically significant at the 2-sided 0.05 level, then the remaining comparisons in the stated hierarchy will be considered descriptive and exploratory.~~		
Section 16.5 Additional Secondary Efficacy Analyses	Additional efficacy analyses will be conducted using PP population.	Additional efficacy analyses will be conducted using **mITT and** PP populations	Addition of mITT population.
Section 16.5.1 Other Histology Endpoints	• Percentage of subjects with changes in fibrosis using the following criteria: o ~~Ishak~~ scoring criteria from Baseline to Month 12 ▪ At least 2 stage improvement o ~~NASH CRN~~ criteria from Baseline to Month 12 ▪ At least 2 stage improvement	• Percentage of subjects with changes in fibrosis using the following criteria: o **NASH CRN scoring system** from Baseline to Month 12 ▪ At least 2 stage improvement o **Ishak scoring** criteria from Baseline to Month 12 ▪ At least **1** stage improvement	Changed ordering of fibrosis scoring system due to modification in primary and secondary efficacy endpoints.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
		▪ **Improvement to Stage 4**	
Section 16.5.1 Other Histology Endpoints	Insertion	[redacted]	Moved from key secondary endpoint to other histology endpoints.
Section 16.5.1 Other Histology Endpoints	Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and ~~baseline fibrosis stage [Ishak 5 or 6]~~. The change in NAS ~~and~~ SAF score will be analyzed using an ANCOVA model at each visit with change from baseline as the dependent variable including treatment group and randomization stratification factor as fixed effects and baseline as a covariate. In addition, changes in NAS and SAF score will be summarized by each category. Overall shift and frequency tables will be presented for NAS score, NAS components, SAF score, and fibrosis scores (according to ~~Ishak,~~ ~~NASH CRN,~~ and Laennec criteria).	Responder endpoints will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and **cryptogenic cirrhosis [yes/no]**. The change in NAS**,** SAF score, and **PCA** will be analyzed using an ANCOVA model at each visit with change from baseline as the dependent variable including treatment group and randomization stratification factor**s** as fixed effects and baseline as a covariate. In addition, changes in NAS and SAF score will be summarized by each category. Overall shift and frequency tables will be presented for NAS score, NAS components, SAF score, and fibrosis scores (according to **NASH CRN, Ishak,** and Laennec criteria).	Clarification due to modification in primary efficacy endpoint.
Section 16.5.2 Clinical Outcomes	Treatment groups will be compared on ~~time to first occurrence of~~ any of the following adjudicated events:	Treatment groups will be compared on **the percentage of subjects who reported** any of the following adjudicated events**, as well as the time to first occurrence:**	Clarification of analysis
Section 16.5.2 Clinical Outcomes	A log rank test stratified by the randomization stratification factor will be used. In addition, treatment groups will be compared on liver-related death.	**For the analysis of time to first occurrence of adjudicated events, a** log rank test stratified by the randomization stratification factor will be used.	Clarification of analysis.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
		In addition, treatment groups will be compared on **each component of the outcome event**s.	
Section 16.5.2 Clinical Outcomes	Insertion	**The percentage of subjects who reported any adjudicated events will be analyzed using a CMH test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and cryptogenic cirrhosis [yes/no]). Percentage of subjects who reported each component of the outcome events will also be analyzed separately in a similar manner.**	Clarification of analysis.
Section 16.9.4 Incidence Endpoints	Insertion	**For the analyses of the percentage of subjects who reported any of the adjudicated clinical outcome events or adjudicated cardiovascular events, all subjects, regardless of whether one has reported any adjudicated events will be included in the denominator, and only subjects with adjudicated events will contribute to the numerator. This represents the proportion of subjects experiencing events to number of subjects at risk.** **Sensitivity analyses may consider all events regardless of adjudication. Events with discrepant adjudication will be analyzed using both results.**	Clarification of endpoint.
Section 16.11 Safety Analyses	Safety ~~data, including AEs and clinical laboratory observations,~~ will be summarized by treatment group using the Safety Population	Safety **evaluations will comprise** treatment-emergent AEs, **adjudicated CV events, vital signs, electrocardiograms (ECGs), and clinical laboratory results.** **Safety data** will be summarized by treatment group using the Safety Population.	Updated to align with the synopsis.

Section	Original Text (Version 1.0)	Revised Text (Version 2.0)	Key Change Reasons/Justification for Change
Section 16.13	Insertion	**The DMC will review the safety data, which will include AE data as well as lab values. PK results will be made available to the DMC as appropriate.** The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review **PK**, safety and efficacy data as well as the adjudication assessments from the 3 adjudication committees listed in Section 16.14.	To further provide clarity for the DMC review of data including safety and PK.
Appendix B Guidance for Elevated Liver Biochemistry Values	Deletion		Drug-induced liver injury criteria were modified in Section 8.2.2.2. This appendix was redundant.