Clinical Study Protocol 747-303

OBETICHOLIC ACID (OCA)

A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis

The REGENERATE Study

RandomizEd Global Phase 3 Study to Evaluate the Impact on NASH with FibRosis of Obeticholic Acid TreatmEnt

Version 11.0: 04 May 2021

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Sponsor

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NCT Number: NCT02548351
This **NCT** number has been applied to the document for purposes of posting on Clinicaltrials.gov

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 747-303. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected subjects according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms, 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 747-303 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the declaration of Helsinki, and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

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

_____
Investigator's Name (Printed)

_____ _____
Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

Medical Monitor

Investigators are encouraged to call the PRA Medical Support Center phone number for the United States and Canada at +1 866 326 5053 or for Europe/Asia/Pacific at +44 179 2525 608, or send an email to the NASH medical monitor email at REGENERATE@prahs.com with safety questions as these lines of contact are monitored 24 hours a day. The following individual medical monitors may also be contacted through the NASH medical monitor hotline and email address.

Primary Contact:	PRA Health Sciences Medical Monitor Team [redacted], MD [redacted], MD [redacted], MD (Lead)
Secondary Contact:	[redacted], MD [redacted], Medical Monitoring, Clinical Development Intercept Pharmaceuticals, Inc.
Email:	[redacted]
Telephone:	[redacted]

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 (6-ECDCA); INT-747

Title of Study:

A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis

Study Center(s):

Up to 400 investigational sites, globally

Studied Period:	**Phase of Development:**
The study is event driven and total duration will be determined by the time required to accrue approximately 291 adjudicated events for the clinical outcomes composite endpoint, in the OCA 25 mg and placebo groups combined, for subjects with fibrosis stage 2 and stage 3, estimated to take approximately 10 years.	Phase 3

Objectives:

Primary Objective Assessed at the Month 18 Interim Analysis:

- To evaluate the effect of OCA compared to placebo on histological improvement in nonalcoholic steatohepatitis (NASH) by assessing the following primary endpoints using NASH Clinical Research Network (CRN) scoring criteria:
  - Improvement in fibrosis by at least 1 stage with no worsening of NASH, OR
  - Resolution of NASH with no worsening of fibrosis

Secondary Objectives Assessed at the Month 18 Interim Analysis:

- To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following using NASH CRN scoring criteria:
  - Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
  - No worsening of fibrosis AND no worsening of NASH
  - Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning)
  - Improvement of fibrosis by at least 2 stages
  - Improvement in nonalcoholic fatty liver disease activity score (NAS) by at least 2 points with no worsening of fibrosis
  - Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
  - Resolution of fibrosis
  - Histological progression to cirrhosis
- To evaluate the effect of OCA compared to placebo on liver biochemistry and markers of liver function

[redacted]

Primary Objective Assessed at End of Study (EOS):

- To evaluate the effect of OCA compared to placebo on 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):
  - Death (all cause)
  - Model of end stage liver disease (MELD) score ≥15
  - Liver transplant
  - 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)
  - Progression to cirrhosis

Secondary Objectives Assessed at EOS:

- To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following endpoints using NASH CRN scoring criteria:
  - Improvement in fibrosis by at least 1 stage with no worsening of NASH
  - NASH resolution with no worsening of fibrosis
  - Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either

- No worsening of fibrosis AND no worsening of NASH
- Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning)
- Improvement of fibrosis by at least 2 stages
- Improvement in NAS by at least 2 points with no worsening of fibrosis
- Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
- Resolution of fibrosis

- To evaluate the effect of OCA compared to placebo on liver biochemistry and markers of liver function

Safety Objectives Assessed at EOS

- To evaluate the effect of OCA compared to placebo on:
  - Incidence of adjudicated cardiovascular events
  - Incidence of adjudicated acute kidney injury (AKI)
  - Incidence of adjudicated events of hepatic injury
  - Long-term safety and tolerability (TEAEs, ECGs, vital signs, clinical laboratory assessments)
- To evaluate the correlation between histology and noninvasive scores of liver fibrosis with clinical outcomes at the end of the study

Methodology:

Study Design

This Phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter international study will evaluate the effect of OCA on histological improvements in NASH, all-cause mortality, and liver-related clinical outcomes. The study will enroll approximately 2370 subjects with NASH. The population will comprise approximately 2085 subjects with biopsy-confirmed, noncirrhotic NASH and evidence of stage 2 or stage 3 liver fibrosis, including approximately 60% with fibrosis stage 3 and approximately 40% with fibrosis stage 2; and an additional cohort of approximately 285 subjects with stage 1 fibrosis with at least 1 accompanying comorbidity to gather information on the safety of OCA and progression of liver disease in this population.

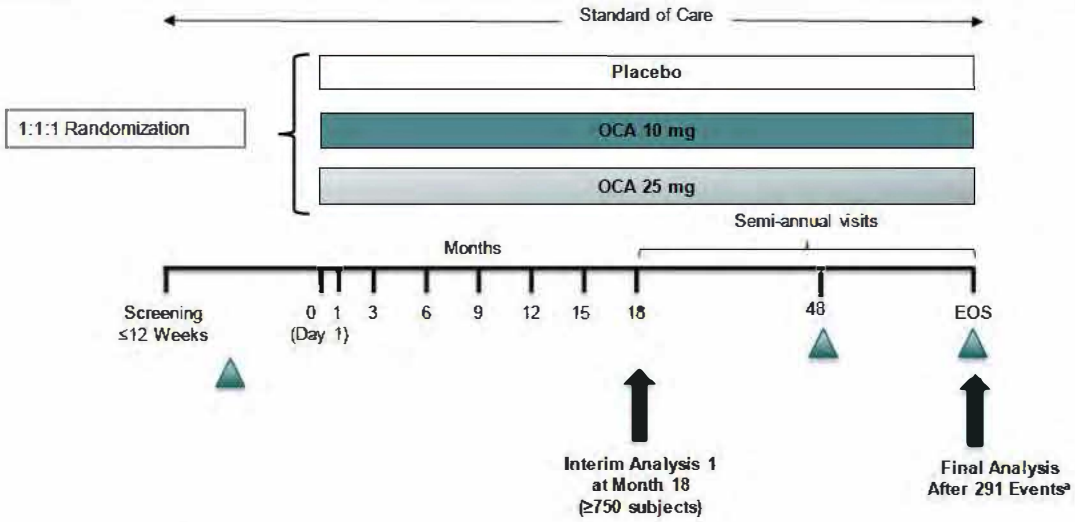
A planned Interim Analysis is to be performed when a minimum of 750 randomized subjects (the first sequential) with fibrosis stage 2 or stage 3 would have reached their actual/planned Month 18. For the purpose of determining the timing of the Month 18 Interim Analysis, subjects that discontinue before their Month 18 visit are considered to have reached their Month 18 Visit and will be part of the Month 18 Interim Analysis cohort. The cutoff for the Month 18 Interim Analysis cohort database lock will be defined in the SAP. The study will be continued in a blinded fashion, and subjects will be followed for clinical outcomes to confirm clinical benefit. Final analysis will evaluate the effect of OCA on mortality and liver-related clinical outcomes and long-term safety of OCA after the accrual of approximately 291 adjudicated clinical outcomes composite events combined in the OCA 25 mg and placebo groups for subjects with fibrosis stage 2 or stage 3 (projected to take

approximately 10 years in total). Subjects are expected to have a minimum follow-up time of approximately 4 years.

Subjects will be screened for a period of up to 12 weeks before entering the study. Approximately 2370 subjects with NASH who meet all eligibility criteria will be randomized to receive OCA 10 mg, OCA 25 mg, or matching placebo in a 1:1:1 ratio for the duration of the study, in conjunction with local standard of care. Randomization of subjects with fibrosis stage 2 or stage 3 will be stratified by presence of type 2 diabetes at enrollment (yes/no) and use of thiazolidinediones (TZDs)/glitazones or vitamin E at baseline (yes/no). Biopsy-confirmed NASH will be determined by central reading of liver histology at Screening, and all subsequent histology assessments will be performed centrally in a blinded fashion.

Investigational product (ie, OCA or placebo) will be taken orally, with water, once daily. Subject safety and laboratory assessments will be evaluated at clinical visits occurring after the first month and once every 3 months following the initiation of treatment (Day 1) through Month 18. Following the Month 18 visit, clinic visits will occur every 6 months for the remaining duration of the study.

With the exception of liver transplant, if a subject experiences a suspected or confirmed clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for discontinuation outlined in the protocol. Subjects who discontinue investigational product are expected to be followed through to study closure (or at the discretion of the Sponsor). Additional strategies to encourage continued subject participation in the study will be outlined in a Subject Retention Plan.



EOS = end of study

▲ Biopsy (Subjects without a liver biopsy performed within 6 months before Day 1 will have a biopsy at the second Screening Visit).

[a] Number of adjudicated events accrued in placebo and OCA 25 mg groups combined.

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 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, between Day 1 and Month 18, unless the baseline therapy is no longer considered clinically appropriate by the Investigator. In general, Investigators will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines.

Exceptions to this general requirement are noted below.

- Subjects providing historical biopsies to determine study eligibility should either not be taking any drugs with potential NASH-modifying properties (specifically, TZDs/glitazones or vitamin E) or should be on a stable dose of these medications for 6 months before Day 1 through Month 18. Changes to these drugs with potential NASH-modifying properties are not permitted for the first 18 months of the study. Ideally, subjects should generally remain on baseline TZDs/glitazones or vitamin E from Month 18 through the end of the study, unless the baseline therapy is no longer considered clinically appropriate by the Investigator.
- Given the prevalence of dyslipidemia in subjects with NASH and the potential increase in total and low-density lipoprotein cholesterol (LDLc) following treatment with OCA, it is recommended that Investigators proactively monitor and manage lipid levels via appropriate medicinal interventions (eg, statins). Recent guidelines stress the importance of evaluating atherosclerotic cardiovascular disease (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.

Prospective Surveillance:

[redacted] screening will include a hepatobiliary ultrasound and alpha-fetoprotein assessment according to the schedule presented in Table 1. For subjects who develop [redacted] during the study, [redacted] screening assessments for study visits after onset of [redacted] are not required.

[redacted]

Liver Histology, 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 and unscheduled biopsies. To determine eligibility at enrollment, a central pathologist must confirm histological presence of NASH and a minimum NAS of 4 with a score of at least 1 in each component of NAS. For each biopsy, key features of NASH and fibrosis staging will be graded in accordance with the NASH CRN criteria for scoring (Kleiner 2005). [redacted].

Event Adjudication: All potential liver-related clinical outcomes and potential events of hepatic injury, AKI, major adverse cardiovascular events (MACE), 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 (CAC): 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 including clinical events and histological findings of potential disease progression to cirrhosis
- 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 CAC, 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 outside of a protocol amendment.

DMC Oversight: An independent DMC will review all safety and efficacy data resulting from the study at periodic intervals. 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 are expected to have considerable experience with clinical study conduct and DMCs before joining the DMC.

Number of Subjects (Planned):

The study will enroll approximately 2370 subjects with NASH. The population will comprise approximately 2085 subjects with biopsy-confirmed, noncirrhotic NASH and evidence of stage 2 or stage 3 liver fibrosis, including approximately 60% with fibrosis stage 3 and approximately 40% with fibrosis stage 2; and an additional cohort of approximately 285 subjects with stage 1 fibrosis with at least 1 accompanying comorbidity to gather information on the safety of OCA and progression of liver disease in this population. At selected investigational sites, approximately 300 subjects will have the option to provide blood samples for measurement of OCA PK concentrations. At selected centers where the devices are available, subjects may participate in [redacted]. At study sites in the United States, subjects will have the option to provide stool samples for microbiome/metabolome analysis only if they provided baseline (Day 1) samples.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

1. Histologic evidence of NASH upon central read of a liver biopsy obtained no more than 6 months before Day 1 defined by presence of all 3 key histological features of NASH with a score of at least 1 for each and a combined score of 4 or greater out of a possible 8 points according to NASH CRN criteria.
2. Histologic evidence of fibrosis stage 2 (perisinusoidal and portal/periportal) or stage 3 (bridging fibrosis) as defined by the NASH CRN scoring of fibrosis, or

   Histologic evidence of fibrosis stage 1a or stage 1b (mild or moderate, zone 3 perisinusoidal) as defined by the NASH CRN scoring of fibrosis if accompanied by ≥1 of the following risk factors:

   - Obesity (BMI ≥30 kg/m^2)
   - Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c [HbA1c] ≥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)
   - ALT >1.5× upper limit of normal (ULN).
3. For subjects with a historical biopsy, is either not taking or is on stable doses of TZDs/glitazones or vitamin E for 6 months before Day 1.
4. Stable body weight (ie, not varying by >10% for at least 3 months) before Day 1.
5. Age ≥18 years.
6. Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below:
   - Barrier method, ie, condom (male or female) with spermicide or diaphragm with spermicide
   - Intrauterine device
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence (defined as refraining from heterosexual intercourse).
7. 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.

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before Screening (significant alcohol consumption is defined as more than 2 units/day for females and more than 4 units/day for males, on average).
2. 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).
3. HbA1c >9.5% within 60 days before Day 1.
4. Evidence of other forms of known 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's 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 [redacted]
   - History of liver transplant, current placement on a liver transplant list, or MELD score >12.
5. Histological presence of cirrhosis.
6. Total bilirubin >1.5 mg/dL (subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL if their conjugated bilirubin is <1.5× ULN).
7. Conjugated bilirubin ≥1.5 x ULN.
8. AST or ALT ≥10× ULN, international normalized ratio (INR) ≥1.4, or serum creatinine ≥1.5 mg/dL.
9. Creatine phosphokinase >5x ULN.
10. Platelet count <100 000/mm^3.
11. LDL ≥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.
12. Inability to safely undergo a liver biopsy.
13. History of biliary diversion.

14. Known positivity for human immunodeficiency virus infection.
15. Subjects with recent history (within 1 year of Day 1) of significant atherosclerotic cardiovascular disease (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 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 atherosclerotic cardiovascular disease and placement of cardiac pacemaker or defibrillator for reasons other than atherosclerotic cardiovascular disease (eg, for treatment of atrial fibrillation subsequent to nodal ablation) is not exclusionary.
16. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign carcinomas).
17. Known substance abuse in the year before Screening.
18. Pregnancy, planned pregnancy, potential for pregnancy (ie, unwillingness to use effective birth control during the study), or current or planned breast feeding.
19. Participated in a clinical research study with any investigational product being evaluated for the treatment of diabetes, weight loss, or NASH in the 6 months before Day 1.
20. Received any investigational product not being evaluated for the treatment of diabetes, weight loss, or NASH 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.
21. Previous exposure to OCA.
22. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study, is uncertain.
23. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
24. Any other condition that, in the opinion of the Investigator, would impede compliance or hinder completion of the study.
25. Acute cholecystitis or acute biliary obstruction.
26. BMI >45 kg/m^2 with at least 1 of the following comorbidities:
    - Hypertension with a blood pressure ≥140/90 mmHg if <60 years, ≥150/90 mmHg if ≥60 years, or on antihypertensive medication
    - Hyperlipidemia defined as LDL cholesterol ≥160 mg/dL, total cholesterol ≥200 mg/dL, or on lipid lowering medication
    - Type 2 diabetes per 2013 American Diabetes Association criteria.

Investigational Product, Dosage, and Mode of Administration:

OCA tablet, 10 mg, oral administration
OCA tablet, 25 mg, oral administration

Reference Therapy, Dosage, and Mode of Administration:

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

Study Duration:

The overall study duration is event driven and will be determined by the time required to achieve approximately 291 adjudicated events for the clinical outcomes composite endpoint in the OCA 25 mg and placebo groups combined for subjects with fibrosis stage 2 and stage 3, estimated to take approximately 10 years.

Interim Analysis Criteria for Evaluation:

Interim Analyses Variables	Assessments
Primary Objective Assessed at the Month 18 Interim Analysis (All Subjects)	
Improvement in fibrosis with no worsening of NASH	A reduction in fibrosis stage of at least 1 with no increase in hepatocellular ballooning, lobular inflammation or steatosis from baseline based on liver biopsy using NASH CRN criteria
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Secondary Objectives Assessed at the Month 18 Interim Analysis (All Subjects)	
Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either	A reduction in fibrosis stage of at least 1 with no increase in hepatocellular ballooning, lobular inflammation or steatosis from baseline based on liver biopsy using NASH CRN criteria AND/OR NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
No worsening of fibrosis AND no worsening of NASH	No increase from baseline in fibrosis stage AND no increase in hepatocellular ballooning, lobular inflammation, or steatosis based on liver biopsy using NASH CRN criteria
Improvement in each key histological feature of NASH	A reduction in score of at least 1 from baseline for steatosis, lobular inflammation, or hepatocellular ballooning based on liver biopsy using NASH CRN criteria
Improvement of fibrosis by at least 2 stages	A reduction from baseline in fibrosis of at least 2 stages at Month 18 based on liver biopsy using NASH CRN criteria
Improvement in NAS by at least 2 points with no worsening of fibrosis	A reduction in NAS by at least 2 points with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject	A reduction from baseline in fibrosis stage of at least 1 and resolution of NASH as defined above
Resolution of fibrosis	A fibrosis stage of 0 based on liver biopsy using NASH CRN criteria
Histological progression to cirrhosis	A fibrosis stage of 4 based on liver biopsy using NASH CRN criteria
Liver biochemistry and markers of liver function	ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets
[redacted]	

[redacted]

Adjudicated cardiovascular events for cardiovascular outcomes assessment	Cardiovascular events including core MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), 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 as defined in Appendix E and included in the CAC charter will be sent to the CAC for adjudication.
Safety and tolerability	TEAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)

[redacted]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] AST = aspartate aminotransferase; [redacted] FGF-19 = fibroblast growth factor 19; [redacted] ; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; [redacted] INR = international normalized ratio; [redacted] LP(a) = lipoprotein(a); MELD = model of end stage liver disease; [redacted]

EOS Criteria for Evaluation:	
End of Study Analyses Variables	**Assessments**
Primary Objective Assessed at EOS (All Subjects)	
Clinical outcomes composite endpoint	Time to first occurrence of any of the following adjudicated events: death (all cause); MELD score ≥15; liver transplant; 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), or spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical

	intervention (eg, diuretics or paracentesis); or progression to cirrhosis
Secondary Objective Assessed at EOS (All Subjects)	
Improvement in fibrosis with no worsening of NASH	A reduction from baseline in fibrosis of at least 1 stage and no increase in hepatocellular ballooning, lobular inflammation or steatosis based on liver biopsy using NASH CRN criteria
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either	A reduction in fibrosis stage of at least 1 with no increase in hepatocellular ballooning, lobular inflammation or steatosis from baseline based on liver biopsy using NASH CRN criteria AND/OR NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
No worsening of fibrosis AND no worsening of NASH	No increase from baseline in fibrosis stage AND no increase in hepatocellular ballooning, lobular inflammation or steatosis based on liver biopsy using NASH CRN criteria
Improvement of fibrosis by at least 2 stages	A reduction from baseline in fibrosis of at least 2 stages based on liver biopsy using NASH CRN criteria
Improvement in each key histological feature of NASH	A reduction in score of at least 1 from baseline for steatosis, lobular inflammation, or hepatocellular ballooning based on liver biopsy using NASH CRN criteria
Improvement in NAS by at least 2 points with no worsening of fibrosis	A reduction in NAS by at least 2 points with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined as both endpoints being met in the same subject	A reduction from baseline in fibrosis stage of at least 1 using NASH CRN criteria and resolution of NASH as defined above
Resolution of fibrosis	A fibrosis stage of 0 based on liver biopsy using NASH CRN criteria
Liver biochemistry and markers of liver function	ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets
[redacted]	

[redacted]

Safety Objectives Assessed at EOS (All Subjects)	
Adjudicated cardiovascular events for cardiovascular outcomes assessment	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). 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 as defined in Appendix E in the protocol and included in the CAC charter will be sent to the CAC for adjudication
Adjudicated events of hepatic injury	Incidence of adjudicated events of hepatic injury
Adjudicated events of acute kidney injury	Incidence of adjudicated events of acute kidney injury
Long-term safety and tolerability	TEAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted]; AST = aspartate aminotransferase; [redacted] CAC = Cardiovascular Adjudication Committee; [redacted]; ECG = electrocardiogram; [redacted] EOS = end of study; [redacted]; MACE = major adverse cardiovascular events; MELD = model of end stage liver disease; [redacted] NAFLD = nonalcoholic fatty liver disease; NFS = NAFLD fibrosis score; TE = transient elastography; TEAE = treatment-emergent adverse event; [redacted]

Statistical Methods:

Enrollment and Randomization

Subjects will be randomized in a 1:1:1 ratio to placebo, OCA 10 mg, or OCA 25 mg. The study will enroll approximately 2370 subjects with NASH. The population will comprise approximately 2085 subjects with biopsy-confirmed, noncirrhotic NASH and evidence of stage 2 or stage 3 liver fibrosis, including approximately 60% with fibrosis stage 3 and approximately 40% with fibrosis stage 2; and an additional cohort of approximately 285 subjects with stage 1 fibrosis with at least 1 accompanying comorbidity to gather information on the safety of OCA and progression of liver disease in this population.

Randomization of subjects with fibrosis stage 2 or stage 3 will be stratified by presence of type 2 diabetes at enrollment (yes/no) and use of TZDs/glitazones or vitamin E at baseline (yes/no).

Primary Analysis Populations (For End-of-Study Analysis)

Intent-to-Treat (ITT) Population:

The ITT Population will include all randomized subjects with fibrosis stage 2 or stage 3 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.

Full Analysis Population:

The Full Analysis Population will include all randomized subjects, all fibrosis stages, who receive at least 1 dose of investigational product (OCA or placebo). Treatment assignment will be based on the randomized treatment.

Per-Protocol (PP) Population:

The 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.

Safety Population:

The Safety Population will include all randomized subjects, all fibrosis stages, 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.

PK Population:

The PK Population will include all OCA subjects who have at least 1 confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours before the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK Population will be used for OCA PK and PK/PD analyses.

Additional information regarding the data cutoff date for the Month 18 Interim Analysis population will be defined in the SAP.

Analyses

Efficacy Analyses:

All efficacy hypothesis testing will be based on the ITT population including only fibrosis stage 2 and stage 3 subjects. Supportive analyses will be conducted using PP population and all fibrosis stages (Full Analysis Population).

The 2-sided alpha allocated to all testing in this single study will be 0.05. The histological endpoints will be tested at the Month 18 Interim Analysis with alpha level of 0.02. The primary clinical outcomes endpoint will be tested with a minimum alpha level of 0.03 and this may be augmented by recycled alpha from the Month 18 interim analysis.

For the Month 18 Interim Analysis, multiplicity adjustment will be implemented to control the type 1 error. Details will be provided in the SAP.

Primary Efficacy Analysis at the Month 18 Interim Analysis:

The primary efficacy analysis for fibrosis improvement at Month 18 will test the following hypotheses using the ITT population (the ITT population for the Month 18 Interim Analysis is not the same as that for the overall study and is defined in the SAP):

- H_{01}: The percentage of subjects with fibrosis improvement by at least 1 stage with no worsening of NASH is equal between placebo and OCA 25 mg.
- H_{11}: The percentage of subjects with fibrosis improvement by at least 1 stage with no worsening of NASH is different between placebo and OCA 25 mg.

The primary efficacy analysis for the resolution of NASH will test the following hypotheses:

- H_{02}: The percentage of subjects with resolution of NASH and no worsening of fibrosis is equal between placebo and OCA 10 mg.
- H_{12}: The percentage of subjects with resolution of NASH and no worsening of fibrosis is different between placebo and OCA 10 mg.

The primary efficacy analyses at the Month 18 Interim Analysis will compare placebo and OCA using a Cochran–Mantel–Haenszel test stratified by the randomization strata (presence of type 2 diabetes at enrollment [yes/no] and use of TZDs/glitazones or vitamin E at baseline [yes/no]). Subjects with missing histology results at Month 18, will be considered non-responders. Post-baseline biopsies at early termination visit (prior to Month 18) will be included in the analysis regardless of the timing of the biopsy.

Secondary Efficacy Analyses at the Month 18 Interim Analysis:

Histology Analysis

Secondary efficacy endpoints at the Month 18 Interim Analysis are:

- Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
- No worsening of fibrosis AND no worsening of NASH

- Percentage of subjects with improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning).
- Percentage of subjects with improvement of fibrosis by at least 2 stages
- Percentage of subjects with improvement in NAS by at least 2 points with no worsening of fibrosis
- Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
- Resolution of fibrosis
- Histological progression to cirrhosis

Primary Efficacy Analysis at EOS:

The primary efficacy endpoint at the end of the study will evaluate the effect of OCA (10 mg and 25 mg) compared to placebo on the clinical outcomes composite endpoint including all-cause mortality and liver-related clinical outcomes, as listed under the objectives for EOS section above. Only adjudicated events will be included in analyses.

The hypothesis test for the clinical outcomes composite endpoint is:

- H_0: The time to first occurrence of any of the adjudicated events including all-cause mortality and liver-related clinical outcomes is equal between placebo and OCA.
- H_1: The time to first occurrence of any of the adjudicated events including all-cause mortality and liver-related clinical outcomes is different between placebo and OCA.

The hypothesis testing for this primary efficacy endpoint at EOS will be conducted with control of Type 1 error (OCA 25 mg, then 10 mg).

Placebo and each OCA dose will be compared separately using a log rank test stratified by the randomization stratification factor. The primary efficacy analyses at EOS will compare placebo and OCA, using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (type 2 diabetes at enrollment [yes/no] and use of TZDs/glitazones or vitamin E at baseline [yes/no]). The hazard ratio and 95% confidence interval will be determined based on a Cox regression model stratified by randomization strata to estimate the magnitude of the effect.

Secondary Efficacy Analyses at EOS:

Histology Analysis

- Improvement in fibrosis by 1 stage or more, with no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis
- NASH resolution with no worsening of fibrosis
- Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
- No worsening of fibrosis AND no worsening of NASH
- Percentage of subjects with improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning).
- Percentage of subjects with improvement of fibrosis by at least 2 stages
- Percentage of subjects with improvement in NAS by at least 2 points with no worsening of fibrosis
- Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
- Resolution of fibrosis

Interim Analyses of Clinical Outcomes Post Month 18 Interim Analysis:

There will be 2 planned interim analyses to be conducted using group sequential approach in accordance to the SAP and DMC Charter at the accumulation of 50% and 80% of the total planned 291 adjudicated clinical

outcome events. The primary efficacy endpoint for these planned interim analyses will be the clinical outcomes composite endpoint.

If either of these 2 interim analyses is significant, then all analyses described in Section 16.4 will be carried out.

Safety Analyses:

Safety data, including TEAEs, adjudicated cardiovascular outcomes including MACE, vital signs, ECGs, and clinical laboratory results will compare OCA (10 mg and 25 mg) and placebo at the Month 18 Interim Analysis and at EOS.

[redacted]

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
A1AT	alpha-1-antitrypsin
ADA	American Diabetes Association
AE	adverse event
AFP	alpha-fetoprotein
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
[redacted]	
AUDIT	Alcohol Use Disorders Identification Test
[redacted]	[redacted]
BAS	bile acid sequestrants
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
[redacted]	
CI	confidence interval
[redacted]	
CMH	Cochran–Mantel–Haenszel
CP	Child-Pugh
CRA	Clinical Research Associate
CRF	case report form
CRN	Clinical Research Network
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Specialist Term	Explanation
DAP	data access plan
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EASD	European Association of the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
EGD	esophagogastroduodenoscopy
[redacted]	[redacted]
EOS	end of study
EOT	End of Treatment
FDA	Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
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
h	hours
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
[redacted]	[redacted]
HCP	healthcare provider
HCV	hepatitis C virus
HDLc	high-density lipoprotein cholesterol
[redacted]	[redacted]
[redacted]	[redacted]
HSAC	Hepatic Safety Adjudication Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation or Specialist Term	Explanation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IIEF-15	International Index of Erectile Function
IL-6	interleukin-6
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator site file
ITT	Intent-to-Treat
IWRS	interactive web response system
IWQoL-Lite	Impact of Weight on Quality of Life-Lite
KM	Kaplan-Meier
LDLc	low-density lipoprotein cholesterol
LP(a)	lipoprotein(a)
LS	least-square
LTF	lost to follow-up
MACE	major adverse cardiovascular events
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model of end stage liver disease
[redacted]	[redacted]
[redacted]	[redacted]
MW	molecular weight
NAFLD	nonalcoholic fatty liver disease
NAS	nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
NCS	not clinically significant
NFS	nonalcoholic fatty liver disease fibrosis score
OCA	obeticholic acid
PAI-1	plasminogen activator inhibitor-1
PBC	primary biliary cirrhosis or primary biliary cholangitis
[redacted]	[redacted]

Abbreviation or Specialist Term	Explanation
PCSK9	proprotein convertase subtilisin/kexin type 9
[redacted]	[redacted]
[redacted]	[redacted]
PLIN2	perilipin 2
PNPLA3	patatin-like phospholipase domain-containing protein, 3
PP	per protocol
PSC	primary sclerosing cholangitis
PT	prothrombin time
PTT	partial thromboplastin time
QTcF	QT interval corrected by the Fridericia's formula
RNA	ribonucleic acid
RR	time between 2 consecutive R waves
SAE	serious adverse event
[redacted]	[redacted]
SAMM50	sorting and assembly machinery component 50 homolog
SAP	statistical analysis plan
SAR	suspected adverse reaction
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TE	transient elastography
[redacted]	[redacted]
TM6SF2	transmembrane 6 superfamily 2
TNF-α	tumor necrosis factor- α
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal
VAS	visual analogue scales
[redacted]	[redacted]
wks	Weeks
[redacted]	[redacted]

5. INTRODUCTION

5.1. Overview of Nonalcoholic Steatohepatitis and Obeticholic Acid

Nonalcoholic fatty liver disease (NAFLD) is considered to be the hepatic manifestation of the 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 histological diseases, which progresses from simple steatosis to nonalcoholic steatohepatitis (NASH). Up to one-third of these 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, [redacted] 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). Patients with NASH develop progressive fibrosis over a period of 4 to 6 years (Pagadala 2012) and 21% to 26% of these patients develop cirrhosis in 8.2 years (Loomba 2013). Between 38% and 45% of patients with NASH who have progressed to cirrhosis develop liver failure in 7 years to 10 years, and 2% to 5% of this population will develop [redacted] per year (World Gastroenterology Organisation 2012). Accumulating evidence suggests that patients with NASH can progress to [redacted], even in absence of apparent cirrhosis (Ertle 2011, Williams 2013).

Despite the seriousness of the disease, especially when advanced fibrosis/cirrhosis is present, there are currently no approved pharmacologic treatments. The current 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), although 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.

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). CDCA is the natural ligand for FXR, which is a nuclear receptor expressed at high levels in the liver, intestine, kidney, and adrenal glands. In the liver, FXR is expressed in hepatocytes, Kupffer cells, and endothelial cells, and at a low level in hepatic stellate cells. Nuclear receptors constitute a family of ligand-activated transcription factors that can either activate or repress a variety of target genes.

OCA's potent FXR agonist effects make it an attractive novel therapeutic agent for NASH due to its multiple FXR-mediated actions, including prevention and reversal of liver fibrosis, anti-inflammatory effects in liver and vasculature, and hepatocyte protection against bile acid-induced cytotoxicity (Adorini 2012, Mudaliar 2013). Thus, there is strong rationale to advance OCA for the treatment of NASH.

5.2. Nonclinical Experience with Obeticholic Acid

Nonclinical studies have shown several potentially beneficial properties of FXR agonism in NASH, including:

Effects of OCA on 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 (Mudaliar 2013, 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 addition, OCA and other FXR agonists are anti-atherogenic and cardioprotective in animal models (Miyazaki-Anzai 2010, Hartman 2009).

Anti-inflammatory and anti-fibrotic effects of OCA:

- OCA exerts direct effects on serum-starved LX2 cells (an immortalized hepatic stellate cell line) to reduce the expression of key fibrotic genes (collagen I, alpha-1 smooth muscle actin, transforming growth factor β-1 and matrix metalloproteinases) (Albanis 2005).
- In primary and cultured hepatocytes treated with pro-inflammatory mediators, OCA exerted direct effects to inhibit pro-inflammatory gene expression (eg, tumor necrosis factor-α [TNF- α], cyclooxygenase-2, and inducible nitric oxide synthase) (Wang 2008).
- FXR activation (with WAY-362450) reduced inflammatory cell infiltration and hepatic fibrosis in a mouse model of NASH (Zhang 2009).
- OCA improves portal hypertension in cirrhosis models (Mookerjee 2015).
- OCA inhibits gastrointestinal inflammation and preserves intestinal barrier function in models of inflammatory bowel diseases (Gadaleta 2011).

In summary, there is strong rationale to advance OCA for the treatment of NASH based on its FXR-mediated hepatoprotective properties and results indicating that OCA improves glycemia by increasing peripheral glucose uptake, enhances glucose-stimulated insulin secretion, and inhibits hepatic lipid synthesis and content while inducing lipid uptake by adipocytes.

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), primary sclerosing cholangitis (PSC), biliary atresia, and other chronic liver diseases. Ocaliva has received marketing authorization in the United States, Europe, and Canada 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. Please see the approved, region-specific labeling for more information including its specific marketing requirements.

The clinical development program for OCA in subjects with NAFLD or NASH includes data from the following 3 studies, as well as 1 ongoing study with no data available yet:

- Study 747-203: A proof-of-concept, Phase 2 study in subjects with type 2 diabetes and 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.
- 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, placebo-controlled study investigating the effect of OCA and atorvastatin treatment on lipoprotein metabolism in subjects with 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 pruritus general) 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 subjects from Study 747-203 withdrew from the study due to pruritus.

The FLINT study demonstrated that OCA 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 that OCA was superior to placebo in improving fibrosis, a strong predictor of liver-related death. OCA treatment was also associated with improvement in markers of hepatocellular injury and some cardiometabolic features, including weight and systolic blood pressure. Salutary effects on weight and blood pressure are important considerations since patients with NASH present with higher cardiovascular risk given the comorbidities of obesity and diabetes. On average, low-density lipoprotein (LDL) cholesterol demonstrated a modest but significant increase in 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 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. 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 ($p = 0.0061$). The number of pruritus-associated 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 LDL metabolism in subjects with NASH to better understand the lipid profile changes observed in the FLINT study. 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 10 mg atorvastatin 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 low-density lipoprotein cholesterol (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.

5.4. 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 has become one of the leading causes of liver transplant (Wong 2020, Younossi 2020), highlighting the need for development of effective therapies that can improve steatohepatitis and resulting fibrosis, potentially delaying liver transplant or death. In the FLINT study, OCA demonstrated statistically significant improvements over placebo in all individual features of steatohepatitis as well as fibrosis (Neuschwander-Tetri 2015) and merits further evaluation in a larger study.

Given the slow natural history of progression for NASH, assessing clinical endpoints is a long-term endeavor. Hence, Study 747-303 is designed to initially assess efficacy based on a surrogate endpoint to support a regulatory filing, and subsequently confirm the ability of OCA to confer clinical benefit over placebo.

Enriching the population for Study 747-303 with a mix of subjects with more advanced and aggressive disease states serves to enroll subjects with the greatest unmet need and at highest risk

of disease progression, and increases the likelihood of accruing outcomes to confirm clinical benefit in a reasonable time frame.

5.4.1. 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 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. Notably, accounting for the standard of care effect is critical when designing an outcome-based study conducted globally when there are regional differences in the treatment of subjects with NASH.

5.4.2. Rationale for OCA Dose

The dose of 25 mg was chosen based on prior studies in subjects with NAFLD and NASH (Study 747-203 and FLINT). In Study 747-203, 64 subjects with type 2 diabetes and NAFLD were treated with placebo, OCA 25 mg or OCA 50 mg for 6 weeks. Both doses were similarly efficacious. Only mild constipation was seen more frequently in the 50 mg OCA group (24%) than the 25 mg OCA and placebo groups (0% each) in this 6-week, proof-of-concept study.

The subsequent, Phase 2 randomized, double-blind FLINT study evaluated OCA 25 mg and placebo in subjects with NASH over 72 weeks. While OCA was well-tolerated overall, there was an increased incidence of mostly mild or moderate pruritus in OCA-treated subjects compared to placebo-treated subjects. 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 the proposed NASH study in addition to the 25 mg dose.

5.5. Summary of Known Potential Risks with Investigational Product

The primary AE shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications, as well as in healthy subjects, with the highest frequency observed in subjects with PBC. 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.

The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk. Recent safety findings in NASH clinical trials include 9 cases of hepatic decompensation 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 an SAE of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis. The fatal case was reported in a subject with cirrhosis and hepatic impairment at baseline; the subject was in the OCA 25 mg treatment group.

Key liver-related findings:

- eDISH analyses show no evidence of hepatic injury with OCA compared to placebo.
- In PBC, hepatic AEs evaluated by Standardized MedDRA criteria showed a rate of hepatic AEs higher in OCA-treated subjects compared with those treated with placebo. In NASH clinical trials, the incidence of hepatic TEAEs was similar between OCA and placebo groups. Serious hepatic TEAEs, however, occurred more frequently with OCA 25 mg, as compared to OCA 10 mg and placebo
- 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 Classification. While 1.5- and 1.7-fold increases in liver concentrations of OCA are predicted for subjects with Child-Pugh Class B and C, respectively, liver concentrations of OCA in subjects with Child-Pugh A are predicted to be similar to those of healthy control subjects (1.1-fold increase). In a hepatic impairment study in NASH subjects with compensated 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).
- Serious liver-related adverse reactions have been reported in postmarketing in PBC patients with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Ocaliva was dosed more frequently than the recommended starting dosage of 5 mg once weekly.

OCA-related changes in serum lipids (decrease in high-density lipoprotein cholesterol [HDLc] and increase in LDLc) have been observed in healthy volunteers, in subjects with PBC and NASH, and in subjects with other underlying conditions. However, the pattern and magnitude, as well as the clinical significance of these changes, are not well understood and clearly depend on a subject's underlying condition and other comorbidities. Although increases in LDLc have generally been considered to be associated with increased cardiovascular risk, it is not possible to draw conclusions regarding the cardiovascular effect of OCA-related changes in lipid profile given the concurrent positive effects of OCA on other metabolic factors such as a decrease in hs-CRP (in PBC studies), and relative improvement of triglyceride and very low-density lipoprotein (VLDL) cholesterol levels. In order to better assess cardiovascular risk, longer treatment periods and larger numbers of subjects are necessary and are being studied further.

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 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.

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.

Refer to the IB 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; 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 subjects necessitating closer surveillance of subjects 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 will consistently and frequently assess individual subjects to determine on an ongoing basis the totality of a subject's clinical profile, which includes careful evaluation of signs and symptoms of potential hepatic injury and/or decompensation coupled with rules-based laboratory monitoring.

Subjects will be monitored for potential hepatic injury and/or decompensation and progression to cirrhosis (Section 7.4). Criteria for implementing dosing adjustments, interruptions, or discontinuations, and close monitoring procedures postdose-adjustment are described in Section 7.4.3 and 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.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective Assessed at Month 18 Interim Analysis

- To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following primary endpoints using NASH CRN scoring criteria:
  - Improvement in fibrosis by at least 1 stage with no worsening of NASH, OR
  - Resolution of NASH with no worsening of fibrosis

6.2. Secondary Objectives Assessed at Month 18 Interim Analysis

- To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following using NASH CRN scoring criteria:

  - Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
  - No worsening of fibrosis AND no worsening of NASH
  - Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning)
  - Improvement of fibrosis by at least 2 stages
  - Improvement in NAFLD activity score (NAS) by at least 2 points with no worsening of fibrosis
  - Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
  - Resolution of fibrosis
  - Histological progression to cirrhosis
- To evaluate the effect of OCA compared to placebo on liver biochemistry and markers of liver function

[redacted]

- Incidence of adjudicated cardiovascular events
- Safety and tolerability (TEAEs, ECGs, vital signs, clinical laboratory assessments)

6.4. Primary Objective Assessed at End of Study

- To evaluate the effect of OCA compared to placebo on 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):
  - Death (all cause)
  - Model of end stage liver disease (MELD) score ≥15
  - Liver transplant
  - 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)
  - Progression to cirrhosis

6.5. Secondary Objectives Assessed at End of Study

- To evaluate the effect of OCA compared to placebo on histological improvement in NASH by assessing the following endpoints using NASH CRN scoring criteria:
  - Improvement in fibrosis by at least 1 stage with no worsening of NASH
  - NASH resolution with no worsening of fibrosis
  - Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
  - No worsening of fibrosis AND no worsening of NASH
  - Improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning)
  - Improvement of fibrosis by at least 2 stages

  - Improvement in NAS by at least 2 points with no worsening of fibrosis
  - Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
  - Resolution of fibrosis
- To evaluate the effect of OCA compared to placebo on liver biochemistry and markers of liver function

6.7. Safety Objectives Assessed at End of Study

- To evaluate the effect of OCA compared to placebo on:
  - Incidence of adjudicated cardiovascular events
  - Incidence of adjudicated acute kidney injury (AKI) events
  - Incidence of adjudicated events of hepatic injury
  - Long-term safety and tolerability (TEAEs, ECGs, vital signs, and clinical laboratory assessments)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This Phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter international study will evaluate the effect of OCA on histological improvements in NASH, all-cause mortality, and liver-related clinical outcomes. The study will enroll approximately 2370 subjects with NASH. The population will comprise approximately 2085 subjects with biopsy-confirmed, noncirrhotic NASH and evidence of stage 2 or stage 3 liver fibrosis, including

approximately 60% with fibrosis stage 3 and approximately 40% with fibrosis stage 2; and an additional cohort of approximately 285 subjects with stage 1 fibrosis with at least 1 accompanying comorbidity to gather information on the safety of OCA and progression of liver disease in this population.

A planned Interim Analysis is to be performed when a minimum of 750 randomized subjects (the first sequential) with fibrosis stage 2 or stage 3 would have reached their actual/planned Month 18 Visit. For the purpose of determining the timing of the Month 18 Interim Analysis, subjects that discontinue before their Month 18 visit are considered to have reached their Month 18 Visit and will be part of the Month 18 Interim Analysis cohort. The cutoff for the Month 18 Interim Analysis cohort database lock will be defined in the SAP. The study will be continued in a blinded fashion, and subjects will be followed for clinical outcomes to confirm clinical benefit. Final analysis will evaluate the effect of OCA on mortality and liver-related clinical outcomes and long-term safety of OCA after the accrual of approximately 291 adjudicated clinical outcomes composite events combined in the OCA 25 mg and placebo groups for subjects with fibrosis stage 2 or stage 3 (projected to take approximately 10 years in total). Subjects are expected to have a minimum follow-up time of approximately 4 years.

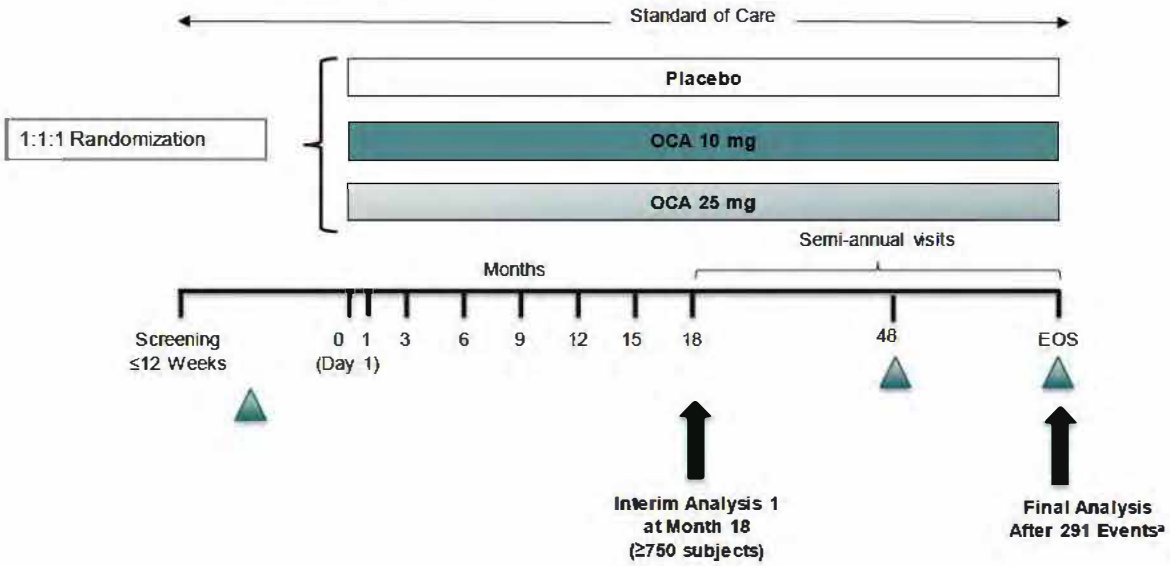
Subjects will be screened for a period of up to 12 weeks before entering the study. Approximately 2370 subjects with NASH who meet all eligibility criteria will be randomized to receive OCA 10 mg, OCA 25 mg, or matching placebo in a 1:1:1 ratio for the duration of the study, in conjunction with local standard of care. Randomization of subjects with fibrosis stage 2 or stage 3 will be stratified by presence of type 2 diabetes at enrollment (yes/no) and use of thiazolidinediones (TZDs)/glitazones or vitamin E at baseline (yes/no). Biopsy-confirmed NASH will be determined by central reading of liver histology at Screening, and all subsequent histology assessments will be performed centrally in a blinded fashion.

Investigational product (ie, OCA or placebo) will be taken orally, with water, once daily. Subject safety and laboratory assessments will be evaluated at clinical visits occurring after the first month and once every 3 months following the initiation of treatment (Day 1) through Month 18. Following the Month 18 visit, clinic visits will occur every 6 months for the remaining duration of the study.

With the exception of liver transplant, if a subject experiences a suspected or confirmed clinical outcomes event, he or she should continue the regular visit schedule and continue taking investigational product as long as the subject has not met any of the criteria for discontinuation outlined in Section 7.7. Subjects who discontinue investigational product are expected to be followed through to study closure (or at the discretion of the Sponsor). Specific strategies to encourage continued subject participation in the study will be outlined in a Subject Retention Plan (Section 7.9).

7.1.1. Study Design Diagram

Figure 1: Study Design Schematic



EOS = end of study
▲ Biopsy (Subjects without a liver biopsy performed within 6 months before Day 1 will have a biopsy at the second Screening Visit).
[a] Number of adjudicated events accrued in placebo and OCA 25 mg groups combined.

7.1.2. Schedule of Study Procedures

Table 1: Schedule of Study Procedures

Study Visit (Relative to Day 1)	Month 0 to Month 18										Month 24 to EOS		
	Screening		0 (Day 1)	1	3	6	9	12	15	18	Semi-Annual/ Annual	Month 48	EOS/ EOT[c]
	1	2[a]											
Visit Window (Relative to Visit Day)	≤12 wks prior[b]			±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	-6 wks to +2 wks	±2 wks	±4 wks	±2 wks[d]
STUDY PROCEDURES – ALL SUBJECTS													
Fast ≥8 h Prior to Visit			X	X	X	X	X	X	X	X	X[e]	X	X
Informed Consent	X												
Medical History	X												
Physical Exam	X									X	X[f]	X	X
12-Lead Electrocardiogram			X							X	X[f]	X	X
Inclusion/Exclusion Criteria	X		X										
Vital Signs and Body Weight[g]	X		X	X	X	X	X	X	X	X	X[e]	X	X
[redacted]	[redacted]		[redacted]			[redacted]		[redacted]		[redacted]			[redacted]
AUDIT, Smoking Habits, Caffeine Consumption	X[i]		X			X		X		X	X[f]	X	X
[redacted]			[redacted]			[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]			[redacted]		[redacted]		[redacted]			
AEs[j]	X	X	X	X	X	X	X	X	X	X	X[e]	X	X
MELD Score	X		X	X	X	X	X	X	X	X	X[e]	X	X
CLINICAL AND LABORATORY EVALUATIONS[s] – ALL SUBJECTS													
Hepatobiliary Ultrasound[k] for [redacted] and Gallbladder Assessment	X[l]		X[m]			X		X		X	X[e]	X	X

Table 1: Schedule of Study Procedures (Continued)

Study Visit (Relative to Day 1)	Month 0 to Month 18										Month 24 to EOS		
	Screening		0 (Day 1)	1	3	6	9	12	15	18	Semi-Annual/ Annual	Month 48	EOS/ EOT[c]
	1	2[a]											
Visit Window (Relative to Visit Day)	≤12 wks prior[b]			±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	-6 wks to +2 wks	±2 wks	±4 wks	±2 wks[d]
AFP for [redacted]	X		X			X		X		X	X[e]	X	X
Liver Biopsy[n,aa]		X				X						X	X
Prior and Concomitant Medications[o]	X		X	X	X	X	X	X	X	X	X[e]	X	X
Randomization/Treatment Assigned			X										
Lifestyle Modification Counseling			X	X	X	X	X	X	X	X	X[e]	X	
Dispense Investigational Product			X	X	X	X	X	X	X	X	X[e]	X	
Administer Investigational Product Onsite[p]			X										
Collect Bottles/Investigational Product Accountability/Compliance				X	X	X	X	X	X	X	X[e]	X	X
Serum Chemistry, Hematology, Coagulation	X		X	X	X	X	X	X	X	X	X[e]	X	X
Educate Subjects on Signs and Symptoms of Potential Hepatic Injury or Decompensation			X	X		X		X		X	X[e,q]		
Educate Subjects on Signs and Symptoms of Intercurrent Illness and/or Potential Adverse Events (Appendix C)											X[e]		
Evaluate Signs and Symptoms of Potential Hepatic Injury or Decompensation (Appendix C)			X	X	X	X	X	X	X	X	X[e,q]	X	X

Table 1: Schedule of Study Procedures (Continued)

Study Visit (Relative to Day 1)	Month 0 to Month 18										Month 24 to EOS		
	Screening		0 (Day 1)	1	3	6	9	12	15	18	Semi-Annual/ Annual	Month 48	EOS/ EOT[c]
	1	2[a]											
Visit Window (Relative to Visit Day)	≤12 wks prior[b]			±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	-6 wks to +2 wks	±2 wks	±4 wks	±2 wks[d]
Evaluate Signs and Symptoms of Intercurrent Illness and/or Potential Adverse Events (Appendix C)											X[e]		X
Assess Subjects per Potential DILI Management and Progression to Cirrhosis[r,aa] Algorithms			X	X	X	X	X	X	X	X	X[e, q]	X	X
Creatine Phosphokinase[ab]	X												
Thyroid Hormone (TSH)			X			X				X	X[f]	X	X
Free Fatty Acids			X	X		X		X		X	X[f]	X	X
[redacted]			[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinalysis	X		X							X	X[e]	X	X
Urine-Based β-hCG Pregnancy Test[t]	X		X	X	X	X	X	X	X	X	X[e]	X	X
[redacted]													

Table 1: Schedule of Study Procedures (Continued)

Study Visit (Relative to Day 1)	Month 0 to Month 18										Month 24 to EOS		
	Screening		0 (Day 1)	1	3	6	9	12	15	18	Semi-Annual/ Annual	Month 48	EOS/ EOT[c]
	1	2[a]											
Visit Window (Relative to Visit Day)	≤12 wks prior[b]			±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	-6 wks to +2 wks	±2 wks	±4 wks	±2 wks[d]
Cardiovascular Risk Scores (FRS, Reynolds score, SCORE, 10-year ASCVD Risk)			X					X		X	X[e]	X	X
[redacted]													
Virology (HCV/HBsAg)	X												
[redacted]													
CLINICAL EVALUATIONS – FOR SUBSET OF SUBJECTS													
[redacted]													
CLINICAL AND LABORATORY EVALUATIONS – FOR SUBSET OF SUBJECTS CONTINUING IN STUDY (NO NEWLY ENROLLED SUBJECTS)													
[redacted]													

Table 1: Schedule of Study Procedures (Continued)

Study Visit (Relative to Day 1)	Month 0 to Month 18										Month 24 to EOS		
	Screening		0 (Day 1)	1	3	6	9	12	15	18	Semi-Annual/ Annual	Month 48	EOS/ EOT[c]
	1	2[a]											
Visit Window (Relative to Visit Day)	≤12 wks prior[b]			±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	-6 wks to +2 wks	±2 wks	±4 wks	±2 wks[d]
[redacted]													

AE = adverse event; AFP = alpha-fetoprotein; ALT = alanine aminotransferase; [redacted];
AST = aspartate aminotransferase; AUDIT = Alcohol Use Disorders Identification Test; β-hCG = beta human chorionic gonadotropin; [redacted]; BMI = body mass index; [redacted]; CP = Child-Pugh; CRF = case report form; DILI = drug-induced liver injury; [redacted]; EOS = end of study; EOT = end of treatment; [redacted]; h = hour; [redacted];
HCV = hepatitis C virus; HBsAg = hepatitis B virus antigen; ICF = informed consent form; IP = investigational product; MELD = model of end stage liver disease; NAFLD = nonalcoholic fatty liver disease; NFS = NAFLD fibrosis score; [redacted]; RNA = ribonucleic acid; wk(s) = week(s); [redacted]

[a] Not required for subjects who have had a biopsy within 6 months before Randomization (Day 1) and can provide unstained slides.
[b] Subjects will be enrolled in the study when informed consent is obtained. Informed consent may be obtained and slides from a historical biopsy may be sent for central reading before conducting Visit 1 assessments and procedures without initiating the ≤12-week Screening Period.
[c] Study procedures and assessments not required if done within 6 months of the EOT/EOS Visit.
[d] For EOS, window is relative to the EOS date announced by the Sponsor, and the visit should be done as soon as possible upon study discontinuation. For EOT, visit should be as near as possible to last dose taken.
[redacted]

[g] Vital signs include body temperature, sitting heart rate, respiratory rate, and sitting blood pressure. [redacted].

[h] Collect waist circumference and hip circumference. Height measured at Screening only. Body weight will be additionally collected at each visit that vital signs are assessed.

[i] AUDIT only.

[j] AEs occurring after signing of the ICF must be entered on the AE CRF.

[k] For subjects who develop [redacted] during the study, [redacted] assessments for study visits after onset of [redacted] are not required.

[l] Hepatobiliary ultrasound for [redacted] and for gall bladder assessments at Screening is not required if data from a recent historic ultrasound (within 3 months of screening) is available.

[m] Ultrasound will be conducted to enhance [redacted] 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.

[n] For subjects who develop potential liver-related clinical outcomes during the study, protocol-specified biopsies for study visits after onset of the potential outcome event may not be required. For any subject who develops an AE of hepatic injury or decompensation, or if cirrhosis is suspected based on criteria other than biopsy or clinical outcomes (see Figure 3), a liver biopsy is recommended and should be discussed with the Medical Monitor.

[o] Prior medications taken within 6 months of Day 1 are to be recorded at Screening and Day 1 only. For all other visits, only concomitant medications are to be recorded.

[redacted]

After Month 18, subjects determined to be at higher risk of progression or decompensation in the judgment of the Investigator may be monitored for signs and symptoms of potential hepatic injury or decompensation more frequently than every 6 months (as frequently as needed) per discretion of the Investigator and upon discussion with the Medical Monitor.

[r] Perform targeted assessment of ascites and hepatic encephalopathy, if necessary.

[s] Instruct the subject to fast overnight (at least 8 hours) before each visit. Fasting is required before all study visits after screening, but water is permitted and subjects should ensure they are hydrated prior to study visits. Refer to Table 12 for a full list of analytes to be tested.

[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. (Additional testing may be conducted where required, regionally.) If a female study participant becomes pregnant while she is enrolled in the clinical study, she must interrupt treatment with investigational product immediately.

[u] Assessed at EOT only for subjects that discontinue investigational product before or on Month 18 Visit.

[v] 2 PK blood samples (one collected at the beginning of the visit and one at the end of the visit) should be collected at each scheduled visit after the Month 18Visit (Section 14.1). In the days leading up to and including the visit day, subjects should maintain the regular daily timing of their IP dose administration (eg, dosing every morning, dosing every afternoon, dosing every evening, etc). If the subject's regular daily dosing time occurs during the site visit, the subject should administer the dose at the study site and the time of dosing should be recorded in the eCRF.

[w] May be completed as soon as Screening Visit 1 through Day 1.

[redacted]

[ab] Additional CPK samples may be collected if ALT, total bilirubin, or ALP are elevated (see Table 2).

7.1.3. Study Duration

The overall study duration is event driven and will be determined by the time required to achieve approximately 291 adjudicated events for the clinical outcomes composite endpoint in the OCA 25 mg and placebo groups combined for subjects with fibrosis stage 2 and stage 3, estimated to take approximately 10 years.

7.2. Number of Subjects

The study will enroll approximately 2370 subjects with NASH. The population will comprise approximately 2085 subjects with biopsy-confirmed, noncirrhotic NASH and evidence of stage 2 or stage 3 liver fibrosis, including approximately 60% with fibrosis stage 3 and approximately 40% with fibrosis stage 2; and an additional cohort of approximately 285 subjects with stage 1 fibrosis with at least 1 accompanying comorbidity to gather information on the safety of OCA and progression of liver disease in this population.

At selected investigational sites, approximately 300 subjects will have the option to provide blood samples for measurement of OCA PK concentrations. At selected centers where the devices are available, subjects may participate in [redacted] measurements. At study sites in the United States, subjects will have the option to provide stool samples for microbiome/metabolome analysis only if they provided baseline (Day 1) samples.

7.3. Treatment Assignment

Subjects will be randomized in a 1:1:1 ratio to receive placebo, OCA 10 mg, or OCA 25 mg (in a blinded manner) from Day 1 through study termination.

7.4. Monitoring and Management of Potential Hepatic Injury and/or Decompensation

AEs, signs and symptoms of potential hepatic injury or decompensation, and laboratory values will be reviewed at regular intervals as described in the following subsections (Section 7.4.1 to Section 7.4.2.1). Based on the assessments of signs and symptoms of hepatic injury (Appendix C) and liver biochemistry, investigational product will be continued, interrupted, or discontinued per criteria discussed in Section 7.7, and close monitoring procedures will be implemented (refer to Section 7.4.3).

In the event of a potential hepatic injury, the subject should be promptly brought into the clinic to undergo a complete evaluation including laboratory assessments, physical examinations, and review of signs and symptoms of potential hepatic injury or decompensation.

The Investigator will educate each subject about recognizing the signs and symptoms of hepatic injury or decompensation and instruct each subject to contact the study site to report the onset of any of the 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.

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:

- Worsening or new pruritus
- Decreased urine output, dizziness, or lethargy

Healthcare Provider (HCP) Interactions will be reported:

- 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 (refer to Section 9.3)
- Laboratory procedures or assessments performed by an HCP

Signs and symptoms of potential hepatic injury or decompensation should be followed by (1) evaluation of liver biochemistry for potential drug-induced liver injury (DILI) (Section 7.4.1), (2) assessment for disease progression to cirrhosis (Section 7.4.2), (3) triggering of investigational product interruption or discontinuation per criteria (Section 7.7), (4) documentation in the AE eCRF or the SAE eCRFs (Section 15.1.5 and Section 15.1.6), and (5) contact with the medical monitor.

7.4.1. 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 16.11. The specific criteria for identification and adjudication of potential hepatic injury events are described in the HSAC charter.

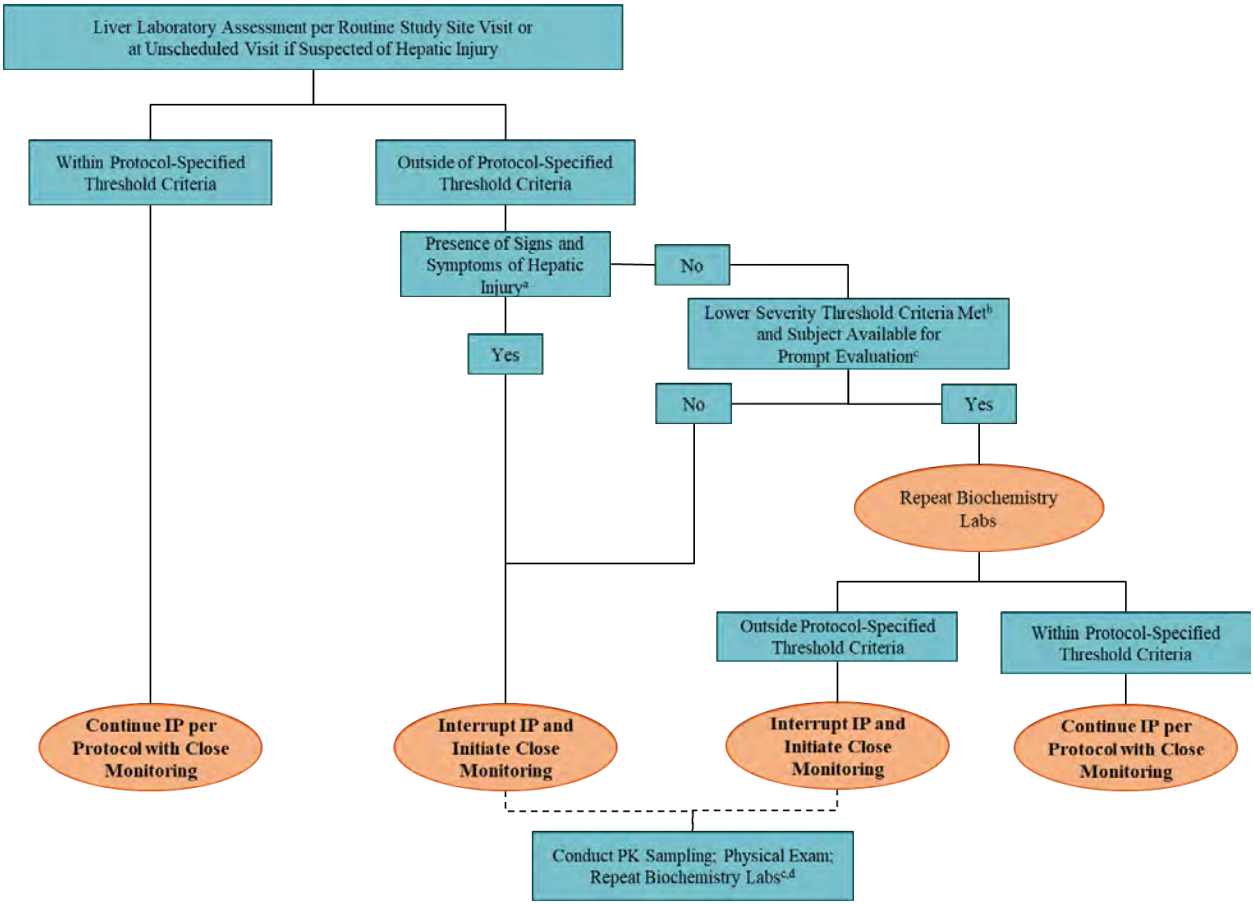
Liver biochemistries will be evaluated to assess biochemical triggers that will prompt an immediate reevaluation of subjects. Thus, these assessments will be performed at:

- Each protocol-specified visit
- Unscheduled visits in the event of signs or symptoms of potential hepatic injury, decompensation, or if laboratory alerts have been triggered

It is important that the laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. 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. 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 subjects using specific 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 2.

Figure 2: Potential DILI Management Algorithm for Study 747-303



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: ALT, ALP, direct and total bilirubin, INR.

[a] Signs and symptoms of hepatic injury include severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, and eosinophilia.

[b] Lower severity treatment-emergent threshold criteria include the following from Table 2:

1) In subjects with normal/near normal ALT at baseline and treatment-emergent ALT ≥5x ULN, TB normal, or with Gilbert's: no change in BL TB
2) In subjects with elevated ALT at baseline and treatment-emergent ALT ≥3x BL or ≥300 U/L, whichever occurs first, TB normal, or with Gilbert's: no change from BL TB
3) In subjects with baseline ALP ≤ULN and treatment-emergent ALP ≥2x BL and >ULN but <250 U/L
4) In subjects with baseline ALP >ULN and treatment-emergent ALP ≥2x BL but <300 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, the Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject.

Table 2: Liver Laboratory Criteria for Monitoring for Potential Hepatic Injury

Baseline	Treatment Emergent	Signs and Symptoms of Hepatic Injury[a]	Action
ALT Normal/Near Normal[b]	ALT ≥5x ULN TB normal Gilbert's[c]: no change in BL TB	No	• Repeat laboratory testing including CPK within 2-4 days
	ALT ≥3x ULN Regardless of TB or DB	Yes	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
	ALT ≥8x ULN Regardless of TB or DB	No	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
	ALT ≥3x ULN TB ≥2x ULN Gilbert's[c]: DB ≥2x ULN or INR >1.5	No	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
ALT Elevated[b]	ALT ≥3x BL or ≥300 U/L, whichever occurs first TB normal Gilbert's[c]: no change from BL TB	No	• Repeat laboratory testing including CPK within 2-4 days
	ALT ≥2x BL or ≥300 U/L, whichever occurs first Regardless of TB or DB	Yes	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
	ALT ≥5x BL or ≥500 U/L, whichever occurs first Regardless of TB or DB	No	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
	ALT ≥2x BL or ≥300 U/L, whichever occurs first TB ≥2x ULN Gilbert's[c]: DB >2x ULN or INR >1.5	No	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
TB (>1.5 mg/dL exclusion criterion 747-303)	TB ≥2.0 mg/dL and DB >30% of TB	Yes/No	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days

Table 2: Liver Laboratory Criteria for Monitoring for Potential Hepatic Injury (Continued)

Baseline	Treatment Emergent	Signs and Symptoms of Hepatic Injury[a]	Action
ALP ≤ULN[d]	ALP ≥2x BL and >ULN	No	*If ALP <250 U/L, then*: • Repeat laboratory testing including CPK within 2-4 days *If ALP ≥250 U/L, then:* **Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
		Yes	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
ALP >ULN[d]	ALP ≥2x BL or >300 U/L, whichever occurs first	No	*If ALP <300 U/L, then*: • Repeat laboratory testing including CPK within 2-4 days *If ALP ≥300 U/L, then:* **Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days
		Yes	**Interrupt** • Repeat laboratory testing including CPK within 2-4 days • Collect PK sample within 7 days

ALP = alkaline phosphatase; ALT = alanine aminotransferase; BL = baseline; DB = direct bilirubin; CPK = creatine phosphokinase; DILI = drug-induced liver injury; INR = international normalized ratio; NASH = nonalcoholic steatohepatitis; OCA = obeticholic acid; PK = pharmacokinetic; TB = total bilirubin; ULN = upper limit of normal

[a] Signs and symptoms of hepatic injury include severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, and eosinophilia.

[b] Baseline ALT is defined as an average of all pre-treatment values from Screening and Day 1. Elevated Baseline defined as ALT ≥1.5x ULN. ALT decreases are common within the first 3-6 months of treatment in NASH subjects receiving OCA. If there is a decrease in ALT for all lab draws through the Month 6 Visit, then a new baseline should be established for subsequent DILI determination, based on the average ALT from the Month 3 and Month 6 Visits.

[c] A subject will be considered to have Gilbert's syndrome if it was established at baseline and documented in the subject's medical history.

[d] Baseline ALP is defined as an average of all pre-treatment values from Screening and Day 1. Modest ALP increases (<50%) from baseline within the first 3 months of treatment are common in NASH subjects receiving OCA and represent an expected pharmacodynamic effect. If there is an increase in ALP through the Month 6 Visit, then a new baseline should be established for subsequent DILI determination, based on the average ALP from the Month 3 and Month 6 Visits.

If any subject meets the triggering threshold limits indicated in Table 2 and experiences signs or symptoms of hepatic injury (severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, eosinophilia) investigational product should be immediately interrupted (see Section 7.7 for dosing modifications).

If no signs or symptoms of hepatic injury 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 2. 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, the Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject.

- If on repeat evaluation, 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 2), 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 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 in whom close monitoring is initiated, a follow-up assessment of the subject's status should be performed after approximately 12 months of monitoring.

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. The original or copies should be retained at the site as the source documents. 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 which case specific guidelines will be provided to the sites for implementation.

7.4.2. Progression of Disease to Cirrhosis

Investigators will closely monitor subjects for potential progression to cirrhosis at every visit (or at unscheduled visits). If the subject meets one or more of the criteria for potential progression to cirrhosis described in Figure 3 and/or any additional evidence that may be available including findings from targeted physical exams or from clinically indicated procedures (eg, biopsy, ultrasound, or esophagogastroduodenoscopy [EGD]), then the subject is considered to have potentially progressed to cirrhosis; Child-Pugh scores must then be assessed. Refer to Section 7.4.2.1 for determination of Child Pugh Score. If a subject may have progressed to cirrhosis, a Fibroscan assessment should be performed where possible (if not already part of the scheduled assessment) and repeated annually. Dose adjustments or investigational product discontinuation may be required in subjects who meet criteria for progression to cirrhosis (see Table 4). If the dose of investigational product is adjusted (Child-Pugh A) or if investigational product is discontinued (Child-Pugh B or C) a PK sample must be collected within 7 days. The PK sample should be collected prior to receiving the reduced dose.

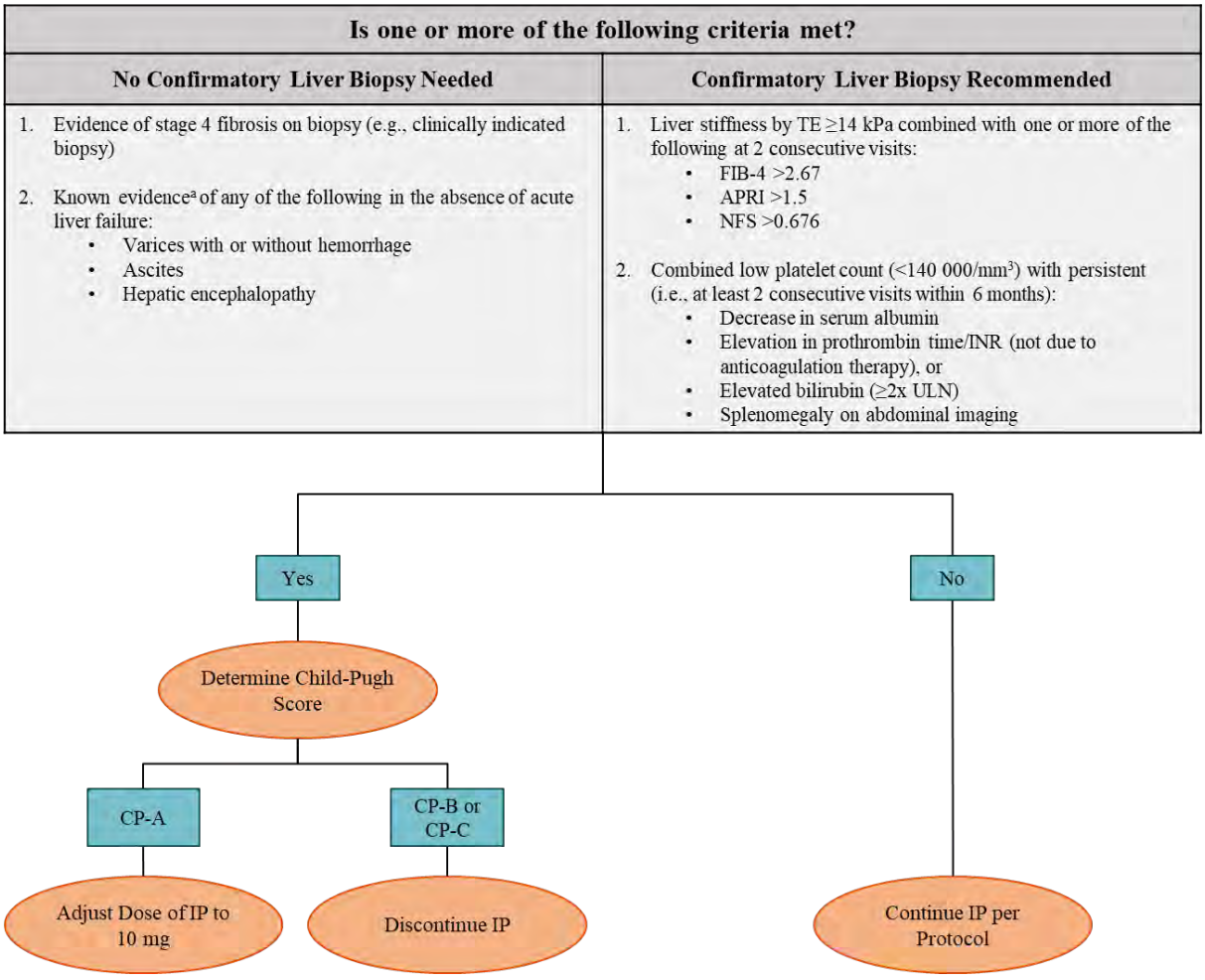
If non-invasive indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy should be obtained and sent for central reading to confirm the diagnosis of cirrhosis and for inclusion in the analysis of study outcomes. Any interpretations by a local pathologist should be collected and entered in the eCRF within 2 days of receiving results. If a biopsy is not performed, the reason should be stated in the eCRF. The following clinical outcomes may preclude the need for a liver biopsy to confirm progression to cirrhosis: presence of ascites, hepatic encephalopathy, variceal hemorrhage, or the presence of large esophageal varices or varices with a red wale that require treatment.

The process for assessing disease progression to cirrhosis, the potential need for liver biopsy, and the implications on dosing are summarized in Figure 3.

Potential events of progression to cirrhosis will be reviewed and adjudicated by the Hepatic Outcomes Committee which is described in Section 16.11. The Hepatic Outcomes Committee

charter describes the specific criteria for identification and adjudication of potential events of progression to cirrhosis.

Figure 3: Algorithm for Determining Progression to Cirrhosis



[redacted]; CP = Child–Pugh; [redacted]; INR = international normalized ratio; IP = investigational product; NFS = nonalcoholic fatty liver disease fibrosis score; TE = transient elastography; ULN = upper limit of normal.

Note: To maintain blinding, dose adjustments will be handled by the investigational product supplier such that:

- Subjects on OCA 25 mg have the dose reduced to OCA 10 mg
- Subjects on OCA 10 mg and placebo remain on OCA 10 mg and placebo, respectively

[a] It is not necessary to rule out the occurrence of varices, ascites, or hepatic encephalopathy at each visit; however, if at any time during the clinical management of the subject there are signs and symptoms that are suggestive of any of these events (eg, ascites noted on ultrasound or presence of varices noted on clinically indicated EGD), then the subject is considered to have met the criteria for progression to cirrhosis and a Child-Pugh screen must be assessed for that subject.

7.4.2.1. Child-Pugh Assessment

The Child-Pugh (CP) Score (Pugh 1973, Lucey 1997) will be assessed only in subjects who meet one or more of the criteria for progression to cirrhosis (Figure 3). A targeted examination will be performed to assess ascites and hepatic encephalopathy. CP is calculated and reported within the electronic data capture (EDC) system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 3 and can range from 5-15. Among subjects who meet criteria for progression to cirrhosis, dose adjustment (see Table 4) should be considered in those

with a CP score <7, and investigational product should be discontinued in those with a CP score ≥7. For the purpose of dose adjustment or discontinuation, Child Pugh Scores should ONLY be applied in subjects who demonstrate progression to cirrhosis based on criteria presented in Section 7.4.2. Dose adjustment or discontinuation should not be considered based solely on the CP score, in subjects who do not meet criteria for progression to cirrhosis.

Calculation of the CP score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the AE review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory. The relationship of CP Score to disease progression is as follows:

- CP Score 5-6 = mild, well compensated disease (ie, CP Class A)
- CP Score 7-9 = moderate, significant functional compromise (ie, CP Class B)
- CP Score ≥10 = severe, decompensated disease (ie, CP Class C)

Table 3: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	µmol/L	<34	34-50	>50
	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	28-35	<28
	g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites[a]		None	Mild	Moderate-Severe
Hepatic encephalopathy[b]		None	Grade 1 or 2	Grade 3 or 4

INR = international normalized ratio
West Haven criteria: Vilstrup 2014; Child-Pugh criteria: Pugh 1973, Lucey 1997.
[a] Refer to CTCAE Appendix D for definitions of severity of ascites
[b] 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

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

MELD is a scoring system used to assess the severity of chronic liver disease. The MELD score is calculated using serum creatinine (mg/dL), bilirubin (mg/dL), and INR. The MELD-Na score is calculated using serum creatinine (mg/dL), bilirubin (mg/dL), INR, and sodium and is calculated when the MELD score is greater than 11. The MELD calculation adjusts for subjects 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.

7.4.3. 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 disease progression to cirrhosis or 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 (Appendix C)
- Liver biochemistry (including ALP, ALT, AST, GGT, total and conjugated bilirubin, creatinine, and albumin), prothrombin time (PT)/INR, serum electrolytes, and assessment of algorithm for progression to cirrhosis (only if the subject is at the study site) 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 7.4.1). A PK sample should also be collected when the dose of investigational product is reduced (Child-Pugh A) or discontinued (Child-Pugh B/C) due to progression to cirrhosis (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 2
- 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; Wilson's disease, 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 in whom close monitoring is initiated for potential hepatic injury, a follow-up assessment of the subject's status should be performed after approximately 12 months of monitoring.

7.4.4. Pruritus

Pruritus is to be closely monitored. Although pruritus itself has not been shown to be a predictor of hepatic injury, Investigators should be vigilant in responding to subjects' complaints of new or worsening pruritus symptoms with prompt follow-up. Pruritus grading (as with all AEs) should be performed in accordance with the current version of the CTCAE (Appendix D).

For subjects with Grade 3 pruritus per the current version of the CTCAE (Section 15.1.5.1), instruct the subject to discontinue investigational product (Table 4). 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 pruritus ≤ Grade 2 is provided in Table 4 and Section 15.1.5.1.

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 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, 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, 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

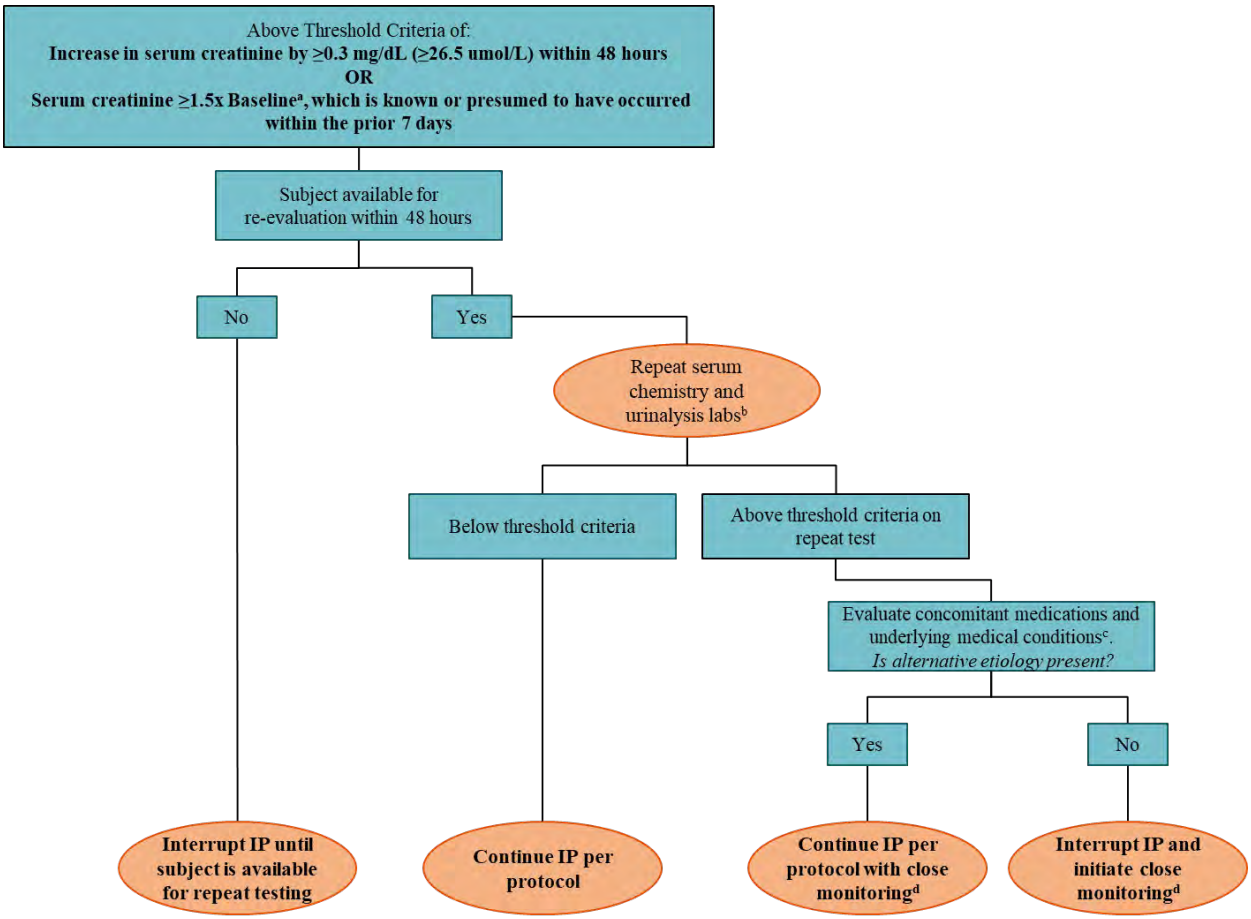
AKI is a serious medical condition that may lead to chronic kidney disease or kidney failure; therefore, it is important to identify and monitor subjects for signs or symptoms suggestive of AKI for appropriate management. Investigators are instructed to evaluate for symptoms suggestive of AKI such as new onset fatigue/asthenia, nausea, or confusion and to assess signs such as decreased skin turgor (dehydration), increased heart rate, lower extremity edema, 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 4.

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.

Figure 4: Algorithm for Monitoring Subjects for Potential Renal Impairment



ACE = angiotensin converting enzyme; AE = adverse event; ARBs = angiotensin receptor blockers; BUN = blood urea nitrogen; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; IP = investigational product; NSAIDS = nonsteroidal anti-inflammatory drugs.

[a] Baseline value is defined as the average of the two most recent serum creatinine values from study visits (scheduled and unscheduled) that are at least 7 days apart and are not associated with an acute event or creatinine increase. Elevated results due to a renal-related AE or transient use of a nephrotoxic medication should not be included in the baseline calculations.

[b] Laboratory assessments include: serum chemistry (creatinine, albumin, BUN, electrolytes), urinalysis with microscopic examination, and assessment of eGFR.

[c] Evaluation should be comprehensive and include assessments of recent medical history, changes in health status, changes in medications (especially ACE inhibitors, ARBs, NSAIDs, diuretics), and intercurrent illness.

[d] 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 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 16.11). 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 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.

7.7. Investigational Product Adjustment, Interruption, and Discontinuation Criteria

Dosages for investigational product should be maintained constant during the study. However, adjustments, interruptions, discontinuation, and any rechallenge of investigational product should be implemented per the criteria outlined in Table 4.

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. The Investigator should use their clinical judgement to determine if more frequent assessments of laboratory tests and symptoms are necessary.
- 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. The Investigator should use their clinical judgement to determine if more frequent assessments of laboratory tests and symptoms are necessary until stabilization of the clinical event leading to discontinuation has occurred (per discretion of the Investigator and upon discussion with the medical monitor [Section 7.4.3]). The subjects will not be rechallenged with investigational product.

Subjects who interrupt treatment will be monitored to determine if or when investigational product may be restarted. However, an interruption of investigational product may result in treatment discontinuation. In this instance, an EOT or EOS visit should occur only after discussion of the event with the sponsor's medical monitor. The investigator should obtain a liver biopsy at the EOT visit to characterize any histological changes during the period that the subject was taking 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 if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.

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.

Table 4: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge

DOSE ADJUSTMENT		
Criteria	**Action Taken with IP**	**Rechallenge**
Progress to cirrhosis and have Child Pugh A cirrhosis (CP score <7)	Adjust to a maximum daily dose of 10 mg (or equivalent placebo) in a blinded fashion	Not applicable. Remain at maximum daily dose of 10 mg (or equivalent placebo) for remainder of study.
≤Grade 2 Pruritus (refer to Section 15.1.5.1)	Drug holiday or less frequent dosing, as needed	Return to original daily dose if tolerated
DOSE INTERRUPTION		
Criteria	**Action Taken with IP[a]**	**Rechallenge[b]**
Liver laboratory values[c] are above the upper threshold criteria and signs and symptoms of hepatic injury are present[d]	Interrupt immediately upon initial observation	Subject may be rechallenged after a minimum of 30 days if abnormal liver enzymes return to below threshold values, there are no symptoms, laboratory abnormalities are determined not to be due to DILI and approved by the Medical Monitor and Investigator. 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.
Liver laboratory values[c] are above the upper threshold criteria and there are no signs and symptoms of hepatic injury[d]	According to threshold limits (Table 2), either interrupt or interrupt after confirmation by repeat testing	
Gastroenteritis (established severe abdominal pain, vomiting, diarrhea) or dehydration	Interrupt	If no evidence of liver injury is detected, IP may be restarted at the same dose after resolution of intercurrent illness.
AE categorized as ≥Grade 4 in severity and not or unlikely related to IP	Interrupt	
Potential renal impairment (serum creatinine exceeds upper threshold criteria [Section 7.6])	Interrupt after confirmation by repeat testing	Subject may be rechallenged after a minimum of 30 days if laboratory results return to within threshold criteria and approved by the Medical Monitor and Investigator.
Symptomatic cholelithiasis and/or cholecystitis	Interrupt	Subjects should remain in the study and complete all protocol-specified assessments, as defined in Table 1, while off IP. Subjects may resume IP: • After full resolution from a cholecystectomy and after receiving approval from the Investigator and Medical Monitor provided there are no signs or symptoms suggestive of retained or recurrent bile duct stones • If it is deemed, after surgical consultation, that the subject does not need to undergo surgery, symptoms have resolved, and after receiving approval from the Investigator and Medical Monitor.

Table 4: Criteria for Dose Adjustment, Interruption, Discontinuation and Rechallenge (Continued)

DOSE INTERRUPTION		
Criteria	**Action Taken with IP[a]**	**Rechallenge[b]**
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 at the discretion of the Investigator and after discussion with the Medical Monitor as described in Section 15.1.12.
DOSE DISCONTINUATION		
Criteria	**Action Taken with IP**	**Rechallenge**
Potential Hepatic Decompensation[e] or Progression to Child Pugh B or C [CP Score ≥7]	Discontinue[g] / 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.
Treatment-emergent acute or nonacute pancreatitis	Discontinue[g] / No Rechallenge	Continue to return for scheduled study visits for safety follow up; however, the subject should not be rechallenged.
≥Grade 3 pruritus[f]		
Other AEs ≥Grade 3 considered possibly, probably, or definitely related to IP		
Liver transplantation		
Bariatric Surgery (Gastric Bypass)		

AE = adverse event; ALP = alkaline phosphatase; ALT = aspartate aminotransferase; CP = Child-Pugh; DILI = drug-induced liver injury; IP = investigational product

[a] If subject is unable to be evaluated promptly, study drug must be immediately interrupted.

[b] Requires complete documentation of full resolution or normal/baseline based on laboratory parameters and symptoms.

[c] ALT, ALP, direct or total bilirubin, or INR.

[d] Signs and symptoms of hepatic injury include severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, and eosinophilia.

[e] Clinically evident complications of portal hypertension (eg, ascites, variceal hemorrhage, hepatic encephalopathy).

[f] Severity per the current version of the CTCAE.

[g] 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. The Investigator should use clinical judgement to determine if more frequent assessments of laboratory tests and symptoms are necessary until stabilization of the clinical event leading to discontinuation has occurred (per discretion of the Investigator and upon discussion with the medical monitor).

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 EOS or EOT Visit. The window of time for scheduling the visit will be based on a final projection of when the requisite 291 adjudicated

events will have been accrued in the OCA 25 mg and placebo groups combined for subjects with fibrosis stage 2 or stage 3.

7.9. Subject Retention

The primary objectives for the end of study analysis are to evaluate the effects of OCA compared with placebo on all-cause mortality and liver-related clinical outcomes. The overall study duration is event driven and will be determined by the time required to observe the prespecified adjudicated events for the clinical outcomes composite endpoint (Section 7.8). Therefore, it is very important that subjects continue to participate for the duration of the study to enable assessment of clinical outcomes.

Subjects may discontinue investigational product during the study; however, these subjects are expected to continue in the study until study termination and every effort will be made by the investigator to discuss subjects' continuation in the study. Investigators will emphasize to subjects the importance of their continuation in the study after withdrawal of investigational product by either continuing to attend regularly scheduled visits, allowing semi-annual telephone visits by the investigator, or by allowing the investigator to have continued access to the subjects' medical records to assess potential major adverse cardiovascular events (MACE) and liver-related clinical outcomes. The site staff will encourage subjects to adopt an option that allows for the most data moving forward. Subjects will be asked to provide both personal and primary physician(s) contact information who can provide information to the investigator about the clinical/medical status on the subjects' behalf. Additional information is described in Section 8.2.1.

Please refer to specific strategies and procedures that will provide additional information to facilitate subject retention as described in a separate Subject Retention Plan.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted at up to 400 international sites with experience in treating patients with 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. Histologic evidence of NASH upon central read of a liver biopsy obtained no more than 6 months before Day 1 defined by presence of all 3 key histological features of NASH with a score of at least 1 for each and a combined score of 4 or greater out of a possible 8 points according to NASH CRN criteria.
2. Histologic evidence of fibrosis stage 2 (perisinusoidal and portal/periportal) or stage 3 (bridging fibrosis) as defined by the NASH CRN scoring of fibrosis, or

Histologic evidence of fibrosis stage 1a or stage 1b (mild or moderate, zone 3 perisinusoidal) as defined by the NASH CRN scoring of fibrosis if accompanied by ≥1 of the following risk factors:

- Obesity (BMI ≥30 kg/m^2)
- Type 2 diabetes diagnosed per 2013 American Diabetes Association criteria (hemoglobin A1c [HbA1c] ≥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)
- ALT >1.5× upper limit of normal (ULN).

3. For subjects with a historical biopsy, is either not taking or is on stable doses of TZDs/glitazones or vitamin E for 6 months before Day 1.
4. Stable body weight (ie, not varying by >10% for at least 3 months) before Day 1.
5. Age ≥18 years.
6. Female subjects of childbearing potential must use ≥1 effective method of contraception during the study and until 30 days following the last dose of investigational product. Effective methods of contraception are considered to be those listed below (refer to Section 9.8 for highly effective contraceptive methods):
   - Barrier method, ie, condom (male or female) with spermicide or diaphragm with spermicide
   - Intrauterine device
   - Vasectomy (partner)
   - Hormonal (eg, contraceptive pill, patch, intramuscular implant or injection)
   - Abstinence (defined as refraining from heterosexual intercourse).
7. 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.

1. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before Screening (significant alcohol consumption is defined as more than 2 units/day for females and more than 4 units/day for males, on average).
2. 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).
3. HbA1c >9.5% within 60 days before Day 1.

4. Evidence of other forms of known chronic liver disease including:
   - Positive test result at Screening for hepatitis B surface antigen (HBsAg)
   - Active hepatitis C virus (HCV) infection (positive for HCV ribonucleic acid [RNA] at Screening) or history of positive HCV RNA test result
   - PBC, PSC, autoimmune hepatitis, or overlap syndrome
   - Alcoholic liver disease
   - Wilson's 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 [LLN] or exclusion at the Investigator's discretion)
   - Prior known drug-induced liver injury within 5 years before Day 1
   - Known or suspected [redacted]
   - History of liver transplant, current placement on a liver transplant list, or MELD score >12.
5. Histological presence of cirrhosis.
6. Total bilirubin >1.5 mg/dL (subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL if their conjugated bilirubin is <1.5× ULN).
7. Conjugated bilirubin ≥1.5 x ULN.
8. AST or ALT ≥10× ULN, international normalized ratio (INR) ≥1.4, or serum creatinine ≥1.5 mg/dL.
9. Creatine phosphokinase >5x ULN.
10. Platelet count <100 000/mm^3.
11. LDL ≥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.
12. Inability to safely undergo a liver biopsy.
13. History of biliary diversion.
14. Known positivity for human immunodeficiency virus infection.
15. Subjects with recent history (within 1 year of Day 1) of significant atherosclerotic cardiovascular disease (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 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 atherosclerotic cardiovascular disease and placement of cardiac pacemaker or defibrillator for reasons other than atherosclerotic cardiovascular disease (eg, for treatment of atrial fibrillation subsequent to nodal ablation) is not exclusionary.

16. Other medical conditions that may diminish life expectancy to <2 years, including known cancers (except carcinomas in situ or other stable, relatively benign carcinomas).
17. Known substance abuse in the year before Screening.
18. Pregnancy, planned pregnancy, potential for pregnancy (ie, unwillingness to use effective birth control during the study), or current or planned breast feeding.
19. Participated in a clinical research study with any investigational product being evaluated for the treatment of diabetes, weight loss, or NASH in the 6 months before Day 1.
20. Received any investigational product not being evaluated for the treatment of diabetes, weight loss, or NASH 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.
21. Previous exposure to OCA.
22. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study, is uncertain.
23. History of known or suspected clinically significant hypersensitivity to OCA or any of its components.
24. Any other condition that, in the opinion of the Investigator, would impede compliance or hinder completion of the study.
25. Acute cholecystitis or acute biliary obstruction.
26. BMI >45 kg/m^2 with at least 1 of the following comorbidities:
    - Hypertension with blood pressure ≥140/90 mmHg if <60 years, ≥150/90 mmHg if ≥60 years, or on antihypertensive medication
    - Hyperlipidemia defined as LDL cholesterol ≥160 mg/dL, total cholesterol ≥200 mg/dL, or on lipid lowering medication
    - Type 2 diabetes per 2013 American Diabetes Association criteria

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. Subjects who permanently discontinue from investigational product are not required to be assessed more frequently than the scheduled study visits provided 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 7.7 for withdrawal criteria related to potential hepatic injury and/or decompensation; progression to cirrhosis; treatment-emergent acute or nonacute

pancreatitis; Grade 3 pruritus, AEs ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product; liver transplantation and bariatric surgery. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.2.1 to Section 8.2.3 below.

Bariatric Surgery (Gastric Bypass)

Subjects must discontinue investigational product after undergoing bariatric surgery. A liver 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.

8.2.1. Other Reasons for Discontinuation of Investigational Product

Subjects who discontinue investigational product are expected to continue in the study until the end of the study or at the discretion of the Sponsor. With the exception of liver transplant, if a subject experiences a suspected or confirmed 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. Specific strategies to encourage continued subject participation in the study will be outlined in a Subject Retention Plan. Early termination procedures should only be conducted if the subject withdraws consent (see Section 9.9.9).

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.
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important.
- 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 or semi-annual telephone contact but allow continued access to medical records to assess for potential major adverse cardiovascular events (MACE) and liver-related clinical outcomes
- Withdrawal of consent:
  - Consent may be fully withdrawn

The Investigator must notify the Medical Monitor as soon as possible when a decision to discontinue a subject from treatment is made or when any subject prematurely withdraws from the study.

8.2.2. Withdrawal of Consent and Requirements to Re-Enter the Study

Withdrawal of Consent

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 must be recorded in the appropriate CRF.

Requirements to Re-enter Study after Withdrawal of Consent

Subjects who withdraw consent and want to re-enter the study must confirm that they have not received any investigational product being evaluated for the treatment of diabetes, weight loss, or NASH within 30 days before restarting investigational product or within 5 half-lives of the compound (whichever was longer) before restarting investigational product. Subjects are to be re-consented and new baseline visit procedures must be performed if the interval from the last visit was more than 3 months (+2 weeks) during the first 18 months of the study or more than 6 months prior (+2 weeks) during the remainder of the study.

8.2.3. 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.

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, as outlined in the Subject Retention Plan. This information and date of contact must be recorded in the appropriate CRF.

8.2.4. Subject Discontinuation Notification

The Investigator must notify the Medical Monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study. The date when the subject is withdrawn and the reason for discontinuation must be recorded in the CRF. If a subject is "lost to follow-up" (fails to return for a visit), a reasonable effort should be made to contact the subject in order to determine why the subject failed to return. This information must be documented in the CRF. If a subject is withdrawn from the study early (regardless of the cause), all of the EOT/EOS evaluations should be performed at the time of withdrawal, as appropriate (see Section 9.9.9).

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, and OCA 25 mg. Each dose will be made up of 1 tablet (ie, one placebo tablet, one OCA 10 mg tablet, or one OCA 25 mg 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.

For subjects participating in the PK portion of the study: All assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the PK assessment, must be completed before administration of investigational product.

Refer to Section 7.7 and Table 4 for adjustments, interruptions, and discontinuation of investigational product per safety criteria.

9.2. Lifestyle Modification Counseling

Despite the serious nature of the disease, there are currently no approved therapies for the treatment of NASH nor accepted standard of care. The therapeutic options for NASH are largely limited to lifestyle modifications, generally encompassing diet and physical activity, and treatment of concurrent conditions such as type 2 diabetes, obesity, hypertension, and dyslipidemia. Lifestyle modifications can be very effective in patients who make significant adjustments to their lifestyle. Therefore, in accordance with the current standard of care, all subjects will receive counseling on lifestyle modification with regard to diet and exercise. Owing to the regional and cultural differences in diet and lifestyle across investigational sites, Investigators will be asked to counsel subjects on ways to maintain a healthy diet and to encourage subjects to engage in an appropriate form of exercise.

9.3. 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 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, between Day 1 and Month 18, unless the baseline therapy is no longer considered clinically appropriate by the Investigator. In general, Investigators will be encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines.

Exceptions to this general requirement are noted below.

- Subjects providing historical biopsies to determine study eligibility should either not be taking any drugs with potential NASH-modifying properties (specifically, TZDs/glitazones or vitamin E) or should be on a stable dose of these medications for 6 months before Day 1 through Month 18. Changes to these drugs with potential NASH-modifying properties are not permitted, for all subjects, for the first 18 months of the study. Ideally, subjects should generally remain on baseline TZDs/glitazones or vitamin E from Month 18 through the end of the study, unless the baseline therapy is no longer considered clinically appropriate by the Investigator.

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 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 15.1.5.1.

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.

9.3.2. Other Concomitant Medications

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 non-invasive indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy should be obtained and sent for central reading (refer to Section 7.4.2).

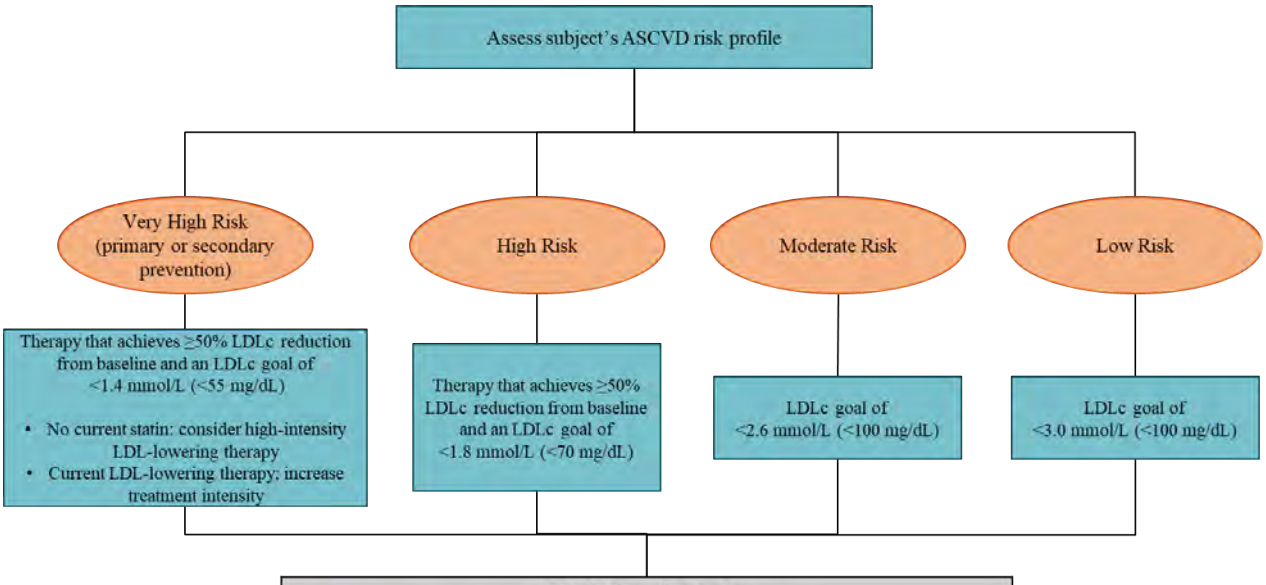
If a study subject receives a COVID-19 vaccination, the date(s) of vaccination, vaccine name, and manufacturer should be recorded as a concomitant medication for each dose (refer to Section 10).

9.3.3. 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 participants as indicated via appropriate medicinal interventions (eg, statins). Recent guidelines stress the importance of evaluating atherosclerotic cardiovascular disease (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 low-density lipoproteins, 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, 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 5).

Figure 5: 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	--

ASCVD = atherosclerotic cardiovascular disease; LDLc = low-density lipoprotein cholesterol.
Adapted from: 2019 ESC/EAS guidelines (Mach 2020).

9.3.4. 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 the 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 an endocrinologist if they experience new onset type 2 diabetes mellitus.

9.4. 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. 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.

9.5. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Subjects will be randomized 1:1:1 to placebo, OCA 10 mg, or OCA 25 mg. Randomization of subjects with fibrosis stage 2 or stage 3 will be stratified by presence of type 2 diabetes at enrollment (yes/no) and use of TZDs/glitazones or vitamin E at baseline (yes/no). The randomization will be based

on a predefined randomization code (generated by the Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based subject registration system at Screening and Day 1. The IWRS will serve as an investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product dispensing information (ie, bottle number[s]) will be provided.

The Sponsor will have access to aggregate event rates (blinded) to perform sample size re-estimation, but will remain blinded to actual adjudicated outcomes throughout the entire study until the final analysis or intervention.

Data flow, access, process and disclosure of unblinded data will be described in a data access plan (DAP) in order to preserve the integrity of the final analysis of the ongoing study.

9.5.1. Emergency Unblinding Procedures

Randomization codes and corresponding treatment assignment will be made available to the Investigator and the Medical Monitor for emergency use only through the IWRS 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 blinded treatment is necessary for further medical management of the subject). If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document in the subject's source record and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment (such as accidental unblinding or unblinding due to a serious adverse event [SAE]). Procedures for unblinding a subject's treatment will be provided separately to the Investigator. The Medical Monitor will document within study correspondence the rationale, circumstances, and the person or persons being informed about the unblinding.

The DMC (refer to Section 16.10) will be provided unblinded data to review during closed sessions. The DMC will document, in the closed session DMC minutes (which will be made available to the Sponsor only after the database is locked and the study is unblinded), details about any unblinded subject data reviews. Cases of premature unblinding (as noted above) will be reviewed by the DMC.

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

9.6. Assignment of Site and Subject Numbers

9.6.1. 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 CRF.

9.6.2. Subject Numbers

Subjects will be identified by a unique 6-digit number, independent of the randomization number. The first 3 digits will represent the site number and the last 3 digits will represent the Screening number.

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 747-303 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).

9.9. Visit Procedures

9.9.1. Visit Windows

Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. For example, Month 3 should ideally occur 3 months (±2 weeks) following Day 1. A month is defined as 4 weeks (ie, 28 days). The visit windows are as follows:

Table 5: Visit Windows and/or Intervals

Visit or Procedure	Visit Window and/or Interval
Screening	Visit(s) are to occur ≤12 weeks before Day 1. Subjects will be enrolled in the study when informed consent is obtained.
Day 1	This is the day of randomization and day of the first dose of investigational product. On-treatment visit scheduling should be calculated from this point going forward unless stated otherwise. [redacted] measurements may be completed as soon as Screening Visit 1 through Day 1.
Month 1	±1 week (7 days)
Months 3 through 15	±2 weeks (14 days)
Month 18	±6 weeks to + 2 weeks (56 days)
Semi-Annual/Annual (Months 24, 30, 36, 42, 54, 60, 66, 72, 78 and continued every 6 or 12 months until the EOS)	±2 weeks (14 days)
Month 48	±4 weeks (28 days)
EOS	±2 weeks (14 days) relative to the EOS date announced by the Sponsor and the visit should be done as soon as possible upon study discontinuation
EOT	Visit should be done as near as possible to last dose taken

EOS = end of study; EOT = end of treatment

Sites should attempt as much as possible to schedule each visit within a 100-day window during the first 18 months of treatment and within the scheduled visit window per protocol based on the Day 1 Visit. If a known visit schedule departure is planned for a time frame greater than 100 days from previous visit during the first 18 months of treatment, an unscheduled bottle should be proactively dispensed and provided to the subject.

9.9.2. Informed Consent Procedures

The Investigator or designee will explain the nature, purpose, possible risk and benefit of the study to the subject and will provide him/her with a copy of the written information and 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 the written information and his/her signed and dated consent form.

Subjects must provide written informed consent if investigational product is re-started after a prolonged interruption of 3 months or more during the first 18 months or after an interruption of more than 6 months at any time after the Month 18 study visit.

9.9.3. Screening Visit Procedures (≤12 weeks before Day 1)

An initial Screening Visit must be performed ≤12 weeks before 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 to confirm that early rescreening will not affect safety or efficacy for the subject. For rescreening, all Screening procedures should be repeated and a new 3-digit Screening number assigned. Subjects should be re-consented, as appropriate, at this time.

Subjects will be enrolled in the study when informed consent is obtained. Screening Visit 1 procedures for all subjects are as follows:

- Review ICFs and obtain signatures before performing any study-related procedures, including Screening procedures
- Collect medical history
- Verify inclusion and exclusion criteria for eligibility
- Perform a physical examination
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- [redacted]
- Determine alcohol consumption (Alcohol Use Disorders Identification Test [AUDIT] questionnaire)
- Assess and record any pretreatment-emergent AEs (after the ICF has been signed)
- Record prior (if within 6 months of Day 1) and current concomitant medications
- Perform hepatobiliary ultrasound for [redacted] screening and for gallbladder assessment unless data from a recent historic ultrasound (within 3 months of screening) is available
- Obtain blood samples for
  - [redacted]
  - Serum chemistry, hematology, and coagulation
  - Creatine phosphokinase
  - Glucose and HbA1c
  - Virology screen (HCV and HBsAg)

- Calculations will be performed by the Sponsor or designee for
  - MELD score
  - [redacted]
- 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 and subjects should ensure they are hydrated prior to study visits)

Screening Visit procedures for a subset of subjects are as follows:

- Provide kits and instructions for collection of stool specimens at home prior to the Day 1 visit (only completed for a subset of subjects enrolled prior to Version 7 of the protocol)
- [redacted]

For subjects without a recent liver biopsy with unstained slides, a second Screening Visit 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).

Laboratory test results must be available and reviewed by the investigator before the liver biopsy.

Screening Visit 2 procedures for all subjects without a recent liver biopsy with unstained slides are as follows:

- Assess and record any pretreatment-emergent AEs
- Obtain liver biopsy

9.9.4. Day 1 Procedures (Randomization)

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 CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- Perform a standard 12-lead electrocardiogram (ECG)
- Review inclusion and exclusion criteria for eligibility
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- [redacted]

- Determine alcohol consumption (AUDIT questionnaire), smoking habits, and caffeine consumption
- Educate subjects about signs and symptoms of potential hepatic injury or decompensation
- Evaluate signs and symptoms of potential hepatic injury or decompensation (Appendix C) and assess subjects per Potential DILI Management (Figure 2) and Progression to Cirrhosis (Figure 3) Algorithms
  - In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample if the site visit is within 7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.
- [redacted]
- Assess and record any pretreatment-emergent AEs
- Record prior (if within 6 months of Day 1) and current concomitant medications
- Randomize the subject only if s/he meets all inclusion criteria and no exclusion criteria
- If hepatobiliary ultrasound for [redacted] and for gallbladder assessment was not performed at Screening and the historic ultrasound is >3 months from Day 1, perform a hepatobiliary ultrasound.
- [redacted]
  - Serum chemistry, hematology, and coagulation
  - Thyroid hormones
  - Free fatty acids
  - Insulin, c-peptide, and HOMA-IR
  - Glucose and HbA1c
  - Apoptosis markers (CK-18 M30 and CK-18 M65)
  - Noninvasive assessments of liver fibrosis: ELF, Fibrotest/Fibrosure
  - Inflammation marker (hs-CRP)
  - [redacted]
- Calculations will be performed by the Sponsor or designee for:
  - MELD score

  - [redacted]

- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Provide lifestyle modification counseling
- Access the IWRS and dispense investigational product. NOTE: All Day 1 assessments, except for the post-dose collection of blood samples for the subset of subjects participating in the PK assessment, must be completed before administration of the first dose of investigational product on Day 1.
- Administer the first 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:
  - To bring the investigational product bottle(s)
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted and subjects should ensure they are hydrated prior to study visits

Day 1 Visit procedures for the various subsets of subjects are as follows:

- [redacted]
- Obtain blood samples for
  - PK assessment

The following Day 1 Visit procedures were only completed for a subset of subjects enrolled prior to Version 7 of the protocol:

- Obtain stool sample (collected at home) for microbiome/metabolome analysis
- [redacted]

9.9.5. Month 1, 3, 9, and 15 Procedures

Month 1, 3, 9, and 15 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 CRF

  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Assess and record AEs
- Review and record concomitant medications
- Obtain blood samples for
  - Serum chemistry, hematology, and coagulation
  - Free fatty acids (Month 1 only)
  - Insulin, c-peptide, and HOMA-IR (Month 1 only)
  - Glucose and HbA1c
  - [redacted]
- Educate subjects about signs and symptoms of potential hepatic injury or decompensation (Month 1 Visit and as frequently as needed per Investigator discretion)
- Evaluate signs and symptoms of potential hepatic injury or decompensation and assess subjects per Potential DILI Management and Progression to Cirrhosis Algorithms
  - In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample if the site visit is within 7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.
- Calculations will be performed by the Sponsor or designee for:
  - MELD score
  - [redacted]
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Provide lifestyle modification counseling
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability
- Access the IWRS and dispense investigational product
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - To swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet

  - To bring the investigational product bottle(s)
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted and subjects should ensure they are hydrated prior to study visits

The following Month 1, Month 3, and Month 15 Visit procedures were only completed for a subset of subjects enrolled prior to Version 7 of the protocol:

- Obtain stool sample (collected at home) for microbiome/metabolome analysis (Month 3 only and only US subjects who provided baseline [Day 1] sample)
- Provide kits and instructions for collection of stool specimens at home at the Month 1 visit for the Month 3 visit and Month 15 visit for the Month 18 visit (Only US subjects who provided baseline [Day 1] sample)

For Months 9 and 15, for subjects participating in the PK assessments, instruct the subject:

- NOT to take investigational product on the morning of the next visit
- To bring the investigational product bottle(s); s/he will dose at the clinic (subjects participating in the PK assessments only)

If non-invasive indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy should be obtained and sent for central reading.

9.9.6. Month 6 and Month 12 Procedures

Month 6 and 12 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 CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- [redacted]
- Determine alcohol consumption (AUDIT questionnaire), smoking habits, and caffeine consumption
- [redacted]
- Perform hepatobiliary ultrasound for [redacted] for gallbladder assessment
- Assess and record AEs
- Review and record concomitant medications
- [redacted]

  - Serum chemistry, hematology, and coagulation
  - Thyroid hormones (Month 6 only)
  - Free fatty acids
  - Insulin, c-peptide, and HOMA-IR
  - Glucose and HbA1c
  - Apoptosis markers (CK-18 M30 and CK-18 M65)
  - Noninvasive assessments of liver fibrosis (ELF, Fibrotest/Fibrosure)
  - Inflammation marker (hs-CRP)
  - [redacted]
- Educate subjects about signs and symptoms of potential hepatic injury or decompensation (as needed, per Investigator's discretion)
- Evaluate signs and symptoms of potential hepatic injury or decompensation and assess subjects per Potential DILI Management and Progression to Cirrhosis Algorithms
  - In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample if the site visit is within 7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.
- Calculations will be performed by the Sponsor or designee for
  - MELD score
  - [redacted]
  - [redacted]
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Provide lifestyle modification counseling
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability
- Access the IWRS and dispense investigational product
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted and subjects should ensure they are hydrated prior to study visits
  - To bring the investigational product bottle(s)

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

Month 6 and 12 Visit procedures for the various subsets of subjects are as follows:

[redacted]

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

If non-invasive indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy should be obtained and sent for central reading.

9.9.7. Month 18 Procedures

Note: Month 18 liver biopsy was performed for subjects who were enrolled in the interim analysis cohort. Subjects randomized on or after 16 Jul 2017 who have not had a Month 18 biopsy are no longer required to have a biopsy at this visit unless progression to cirrhosis is suspected.

Month 18 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 CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- Perform a physical examination
- Perform a standard 12-lead ECG
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- [redacted]
- Determine alcohol consumption (AUDIT questionnaire), smoking habits, and caffeine consumption
- [redacted]

- Perform hepatobiliary ultrasound for [redacted] screening and for gallbladder assessment
- Assess and record AEs
- Review and record concomitant medications

[redacted]

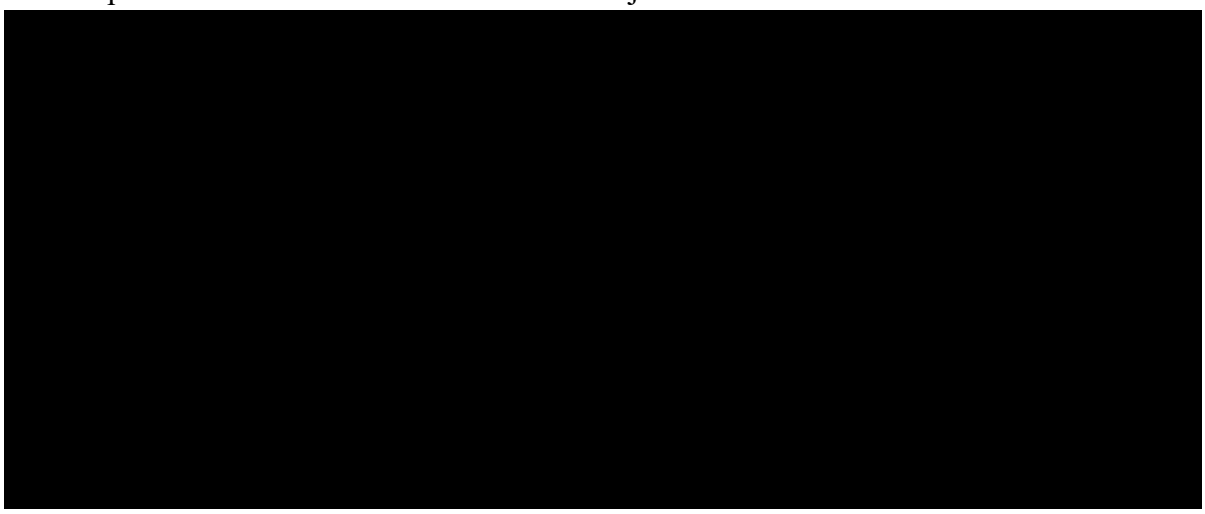
  - Serum chemistry, hematology, and coagulation
  - Thyroid hormones
  - Free fatty acids
  - Insulin, c-peptide, and HOMA-IR
  - Glucose and HbA1c
  - Apoptosis markers (CK-18 M30 and CK-18 M65)
  - Noninvasive assessments of liver fibrosis (ELF, Fibrotest/Fibrosure)
  - Inflammation marker (hs-CRP)
  - [redacted]
- Educate subjects about signs and symptoms of potential hepatic injury or decompensation (as needed, per Investigator's discretion)
- Evaluate signs and symptoms of potential hepatic injury or decompensation and assess subjects per Potential DILI Management and Progression to Cirrhosis Algorithms
  - In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample within 7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.
- Calculations will be performed by the Sponsor or designee for
  - MELD score

[redacted]

- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Provide lifestyle modification counseling
- Collect used bottles of investigational product, assess investigational product compliance, and perform investigational product accountability

- Access the IWRS and dispense investigational product
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted and subjects should ensure they are hydrated prior to study visits
  - To bring the investigational product bottle(s)
- Instruct the subject to swallow the tablet whole with water; s/he must not chew, divide, or crush the tablet.

Month 18 Visit procedures for the various subsets of subjects are as follows:



- Obtain stool sample (collected at home) for microbiome/metabolome analysis (only completed for a subset of US subjects who provided baseline [Day 1] sample and were enrolled prior to Version 7 of the protocol)

For subjects who develop potential liver-related clinical outcomes during the study, protocol-specified biopsies for study visits after onset of the potential outcome event may not be required. For subjects who develop [redacted] during the study, [redacted] assessments for study visits after onset of [redacted] are not required.

9.9.8. Semi-Annual Visit Procedures

If clinical indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy be obtained and sent for central reading.

9.9.8.1. Semi-Annual Procedures (Months 24, 30, 36, 42, 48, 54, 60, 66, 72, 78 and every 6 months until the EOS)

After Month 18, subjects determined to be at higher risk of progression or decompensation in the judgment of the Investigator may be monitored for signs and symptoms of potential hepatic

injury or decompensation as frequently as needed per discretion of the Investigator and upon discussion with the Medical Monitor.

Semi-Annual Visit procedures for all subjects are as follows:

- In the days leading up to and including the visit day, subjects should maintain the regular daily timing of their investigational product dose administration (eg, dosing every morning, dosing every afternoon, dosing every evening, etc). If the subject's regular daily dosing time occurs during the site visit, the subject should administer the dose at the study site and the time of dosing should be recorded in the eCRF.
- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Assess and record AEs
- Review and record concomitant medications
- [redacted]
- Perform hepatobiliary ultrasound for [redacted] and for gallbladder assessment
- Obtain blood samples for
  - [redacted]
  - Serum chemistry, hematology, and coagulation
  - Glucose and HbA1c
  - PK (2 sparse samples): the first sample should be collected when the subject arrives at the study site and the second sample should be collected at the end of the study visit. The times of the last dose of investigational product, the last meal, and collection of the 2 sparse samples will be recorded in the eCRF.
- Educate subjects about signs and symptoms of hepatic injury or decompensation (as needed, per Investigator's discretion) and intercurrent illness and/or potential adverse events (Appendix C)
- Evaluate signs and symptoms of hepatic injury or decompensation and assess subjects per Suspected DILI Management and Progression to Cirrhosis Algorithms intercurrent illness and/or potential adverse events (Appendix C)
  - In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample within

7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.

- Calculations will be performed by the Sponsor or designee for:
  - MELD score
  - [redacted]
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Provide lifestyle modification counseling
- Collect used bottles of investigational product, assess investigational product compliance and perform investigational product accountability
- Access the IWRS and dispense investigational product
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - To bring the investigational product bottle(s)
  - To fast overnight (at least 8 hours) before the next visit, but water is permitted and subjects should ensure they are hydrated prior to study visits

For subjects who develop [redacted] during the study, [redacted] assessments for study visits after onset of [redacted] are not required.

9.9.8.2. Month 48 Visit Procedures

Subjects determined to be at higher risk of progression or decompensation in the judgment of the Investigator may be monitored for signs and symptoms of potential hepatic injury or decompensation as frequently as needed per discretion of the Investigator and upon discussion with the Medical Monitor.

- Verify that the subject has fasted for at least 8 hours
  - Record fasting status in the source and CRF
  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- Perform a physical examination
- Perform a standard 12-lead ECG
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- Determine alcohol consumption (AUDIT questionnaire), smoking habits, and caffeine consumption
- [redacted]

- Perform hepatobiliary ultrasound for [redacted] and for gallbladder assessment
- Obtain liver biopsy
- Assess and record AEs
- Review and record concomitant medications

[redacted]

  - Serum chemistry, hematology, and coagulation
  - Thyroid hormones
  - Free fatty acids
  - Insulin, c-peptide, and HOMA-IR
  - Glucose and HbA1c
  - Noninvasive assessments of liver fibrosis: ELF, Fibrotest/Fibrosure
  - Inflammation marker (hs-CRP)
- Evaluate signs and symptoms of potential hepatic injury or decompensation and assess subjects per potential DILI Management and Progression to Cirrhosis Algorithms
  - In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample within 7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.
- Calculations will be performed by the Sponsor or designee for
  - MELD score

[redacted]

- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Provide lifestyle modification counseling
- Collect used bottles of investigational product, assess investigational product compliance and perform investigational product accountability
- Access the IWRS and dispense investigational product
- Schedule the next visit, reiterate dosing instructions, and advise the subject:
  - To bring the investigational product bottle(s)

– To fast overnight (at least 8 hours) before the next visit, but water is permitted and subjects should ensure they are hydrated prior to study visits

Month 48 Visit procedures for the various subsets of subjects are as follows:

For subjects who develop potential liver-related clinical outcomes during the study, protocol-specified biopsies for study visits after onset of the potential outcome event may not be required.

9.9.8.3. Additional Annual Procedures (Months 30, 42, 54, 66, 78 and every 12 Months until the EOS)

For Months 30, 42, 54, 66, 78 and every 12 months until the EOS the following Annual Visit procedures are to be conducted in addition to those specified in Section 9.9.8.1 for all subjects as follows:

- Perform a physical examination
- Perform a standard 12-lead ECG
- Determine alcohol consumption (AUDIT questionnaire), smoking habits, and caffeine consumption
- Obtain blood samples for
  - Thyroid hormones
  - Free fatty acids
  - Insulin, c-peptide, and HOMA-IR
  - Inflammation marker (hs-CRP)
- Calculations will be performed by the Sponsor or designee for
  - Cardiovascular risk scores (FRS, Reynolds score, SCORE, 10-year ASCVD Risk)

Annual procedures for the various subsets of subjects are as follows:

9.9.9. End of Study and/or End of Treatment Procedures for Subjects that Withdraw from Investigational Product or Withdraw Consent

Subjects who discontinue investigational product are expected to continue in the study until the end of the study or at the discretion of the Sponsor. Additional strategies to encourage continued subjects participation in the study will be outlined in a Subject Retention Plan.

EOT procedures will be required whenever subjects discontinue treatment with investigational product. The EOT visit and procedures listed below must be performed as close as possible to the subject's last dose of investigational product. When a subject discontinues investigational product but continues with regularly scheduled study visits, the EOS visit will be completed later

in the study as the subject's final study visit. The actual investigational product discontinuation scenario (Table 6) will determine the sequence of the EOT and EOS visits and procedures. In some cases, the EOT visit and procedures will precede the EOS visit; in others, the EOT and EOS visits will be combined and performed as close as possible to the subject's last dose of investigational product.

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

Table 6: Early Discontinuation Scenarios

	Investigational Product	Consent	Study Visit Status	EOT Visit[a]	EOS Visit[a]
Early Termination	Discontinued	Withdrawn	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product	
Treatment Discontinuation	Discontinued	Active	Regular Visit Schedule	Complete as close as possible to last dose of investigational product	Complete at final study visit
	Discontinued	Semi-annual contact[b]	Telephone contact every 6 months (±2 weeks)	Combined visit, completed as close as possible to last dose of investigational product	
	Discontinued	Record review only[b]	Record review only	Combined visit, completed as close as possible to last dose of investigational product	
Sponsor Termination	Discontinued	N/A	No additional visits except EOT/EOS	Combined visit, completed as close as possible to last dose of investigational product	
Lost to Follow-Up	Discontinued	LTF	None	Unable to complete due to LTF status	

EOS = end of study; EOT = end of treatment; LTF = lost to follow-up

[a] Refer to Section 9.9.9 and Schedule of Study Procedures for all procedures and evaluations required at the EOS and EOT Visits.

[b] Outcomes data to be discussed or collected include data related to adjudicated event-related data. No additional data (eg, AE, concomitant medication, etc.) data will be collected, except as indicated in Section 15.1.9.

Some assessments noted below may be omitted if they have been completed within 6 months (or the timeframe otherwise specified) and so long as safety issues do not warrant repeat testing.

EOS and/or EOT 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 CRF

  - If the subject reports having eaten within 8 hours, document accordingly in the source and CRF and remind the subject that fasting is required before all study visits after screening.
- Perform a physical examination
- Perform a standard 12-lead ECG
- [redacted] and vital signs (body temperature, sitting heart rate, respiratory rate, and sitting blood pressure)
- [redacted]
- Determine alcohol consumption (AUDIT questionnaire), smoking habits, and caffeine consumption
- Assess and record AEs
- Review and record concomitant medications
- [redacted]
- Perform hepatobiliary ultrasound for [redacted] and for gallbladder assessment (not required at EOT/EOS if done within 6 months of visit)
- Obtain liver biopsy (not required if biopsy has been done within 6 months of the EOT/EOS Visit)
- [redacted]
  - Serum chemistry, hematology, and coagulation
  - Thyroid hormones
  - Free fatty acids
  - Insulin, c-peptide, and HOMA-IR
  - Glucose and HbA1c
  - [redacted]
  - Apoptosis markers (CK-18 M30 and CK-18 M65; only for subjects that discontinue investigational product before or on Month 18 visit)
  - Noninvasive assessments of liver fibrosis: ELF, Fibrotest/Fibrosure
  - Inflammation marker (hs-CRP)
  - [redacted]

- Evaluate signs and symptoms of hepatic injury or decompensation and assess subjects per Suspected DILI Management and Progression to Cirrhosis Algorithms and intercurrent illness and/or potential adverse events (Appendix C)
- Calculations will be performed by the Sponsor or designee for
  - MELD score
  - [redacted]
  - [redacted]
- Obtain urine sample for urinalysis
- Perform a urine-based β-hCG pregnancy test for females of childbearing potential
- Collect all used and unused bottles of investigational product, assess investigational product compliance, and perform investigational product accountability

EOS and/or EOT Visit procedures for the various subsets of subjects are as follows:

- [redacted]
- Obtain stool sample (collected at home or in office if the subject did not receive a kit and instructions at the last visit) for microbiome/metabolome analysis (only completed for a subset of US subjects who provided baseline [Day 1] sample and were enrolled prior to Version 7 of the protocol)

For subjects who develop potential liver-related clinical outcomes during the study, protocol-specified biopsies for study visits after onset of the potential outcome event may not be required. For subjects who develop [redacted] during the study, [redacted] assessments for study visits after onset of [redacted] are not required.

9.9.10. Unscheduled Safety Visit

The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted (refer to Section 7.4). Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. Evaluations may include a physical exam, serum biochemistry, serum electrolytes, assessment of MELD scores, and imaging and/or Fibroscan at Investigator's discretion. In these cases, where a local laboratory is used, it is important that all local laboratory data, including the reference ranges, are collected and entered in the eCRF within 2 days of receiving results. Further monitoring outside of regular scheduled visits should be based on the Investigator's assessment of the subject's clinical status.

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 within 2 days of receiving results. ***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 of direct and total bilirubin, AST, ALT, GGT, ALP, coagulation panel (INR, aPTT), platelets,

albumin and serum creatinine and non-liver safety labs of CBC & Diff, standard electrolytes, lipid panel 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 the 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 the pediatric population suffering from biliary atresia (BA), there are no safety data available specific to use of COVID-19 vaccines in PBC, NASH subjects or in children suffering from BA.

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

11. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

11.1. Investigational Product

The investigational product is a white, round, film-coated tablet containing 25 mg or 10 mg of OCA or placebo. All tablets are identical in size and appearance. The tablets contain the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The OCA 25 mg tablet also contains silicon dioxide.

11.2. Investigational Product Packaging and Labeling

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 will be provided as tablets for oral administration and provided in high-density polyethylene bottles with heat induction seals and child resistant closures. 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 drug is dispensed. If a known visit schedule departure is planned for a time frame greater than 100 days from previous visit during the first 18 months of treatment, an unscheduled bottle should be proactively dispensed and provided to the subject.

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

All OCA tablet strengths provided to clinical trial sites in support of clinical study are to be shipped and stored at 15°C to 25°C. Temperature excursions within the range of 2°C and 30°C for no more than a 6 month period are acceptable, and the OCA tablet continues to be suitable for use in clinical studies. Additionally, temperature excursions within the range -20°C to 40°C for no more than 7 days are acceptable, and the OCA tablet continues to be suitable for use in clinical studies.

11.4. Investigational Product Administration

Refer to Section 9.1.

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

The assessments supporting the objectives for the Interim Analysis at Month 18 are as follows:

Interim Analyses Variables	Assessments
Primary Objective Assessed at the Month 18 Interim Analysis (All Subjects)	
Improvement in fibrosis with no worsening of NASH	A reduction in fibrosis stage of at least 1 with no increase in hepatocellular ballooning, lobular inflammation, or steatosis from baseline based on liver biopsy using NASH CRN criteria
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Secondary Objectives Assessed at the Month 18 Interim Analysis (All Subjects)	
Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either	A reduction in fibrosis stage of at least 1 with no increase in hepatocellular ballooning, lobular inflammation or steatosis from baseline based on liver biopsy using NASH CRN criteria AND/OR NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
No worsening of fibrosis AND no worsening of NASH	No increase from baseline in fibrosis stage AND no increase in hepatocellular ballooning, lobular inflammation or steatosis based on liver biopsy using NASH CRN criteria
Improvement in each key histological feature of NASH	A reduction in score of at least 1 from baseline for steatosis, lobular inflammation, or hepatocellular ballooning based on liver biopsy using NASH CRN criteria
Improvement of fibrosis by at least 2 stages	A reduction from baseline in fibrosis of at least 2 stages based on liver biopsy using NASH CRN criteria
Improvement in NAS by at least 2 points with no worsening of fibrosis	A reduction in NAS by at least 2 points with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject	A reduction from baseline in fibrosis stage of at least 1 using NASH CRN criteria and resolution of NASH as defined above
Histological progression to cirrhosis	A fibrosis stage of 4 based on liver biopsy using NASH CRN criteria

Interim Analyses Variables	Assessments
Resolution of fibrosis	A fibrosis stage of 0 based on liver biopsy using NASH CRN criteria
Liver biochemistry and markers of liver function	ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets
[redacted]	
Adjudicated cardiovascular events for cardiovascular outcomes assessment	Cardiovascular events including core MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), 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 as defined in Appendix E and included in the CAC charter will be sent to the CAC for adjudication
Safety and tolerability	TEAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)
[redacted]	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAC = Cardiovascular Adjudication Committee; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; INR = international normalized ratio; MELD = model of end stage liver disease; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD Activity Score; NASH = nonalcoholic steatohepatitis; NFS = NAFLD fibrosis score; PD = pharmacodynamic; PK = pharmacokinetic; TEAE = treatment-emergent adverse event;

The assessments supporting the objectives for the final analysis at the end of the study are as follows:

EOS Analyses Variables	Assessments
Primary Objective Assessed at EOS (All Subjects)	
Clinical outcomes composite endpoint	Time to first occurrence of any of the following adjudicated events: death (all cause); MELD score ≥15; liver transplant; 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), or spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis); or progression to cirrhosis
Secondary Objectives Assessed at EOS (All Subjects)	
Improvement in fibrosis with no worsening of NASH	A reduction in fibrosis stage of at least 1 and no increase in hepatocellular ballooning, lobular inflammation, or steatosis from baseline based on liver biopsy using NASH CRN criteria
Resolution of NASH with no worsening of fibrosis	NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either	A reduction in fibrosis stage of at least 1 with no increase in hepatocellular ballooning, lobular inflammation or steatosis from baseline based on liver biopsy using NASH CRN criteria AND/OR NASH resolution defined as the overall histopathologic 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 with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
No worsening of fibrosis AND no worsening of NASH	No increase from baseline in fibrosis stage AND no increase in hepatocellular ballooning, lobular inflammation or steatosis based on liver biopsy using NASH CRN criteria
Improvement in each key histological feature of NASH	A reduction in score of at least 1 from baseline for steatosis, lobular inflammation, or hepatocellular ballooning based on liver biopsy using NASH CRN criteria
Improvement of fibrosis by at least 2 stages	A reduction from baseline in fibrosis of at least 2 stages based on liver biopsy using NASH CRN criteria
Improvement in NAS by at least 2 points with no worsening of fibrosis	A reduction in NAS by at least 2 points with no increase in fibrosis stage from baseline based on liver biopsy using NASH CRN criteria
Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject	A reduction from baseline in fibrosis stage of at least 1 using NASH CRN criteria and resolution of NASH as defined above
Resolution of fibrosis	A fibrosis stage of 0 based on liver biopsy using NASH CRN criteria
Liver biochemistry and markers of liver function	ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets
[redacted]	

[redacted]	
Safety Objectives at EOS (All Subjects)	
Adjudicated cardiovascular events for cardiovascular outcomes assessment	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). 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 as defined in Appendix E and included in the CAC charter will be sent to the CAC for adjudication
Adjudicated events of AKI	Evaluate the effect of OCA compared to placebo on the incidence of adjudicated AKI events
Adjudicated events of hepatic injury	Evaluate the effect of OCA compared to placebo on the incidence of adjudicated events of hepatic injury
Long-term safety and tolerability	TEAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)

AKI = acute kidney injury; ALT = alanine aminotransferase; [redacted]; AST = aspartate aminotransferase; [redacted]; CAC = Cardiovascular Adjudication Committee; [redacted]; ECG = electrocardiogram; [redacted] Fibrosis; EOS = end of study; [redacted]; MACE = major adverse cardiovascular events; MELD = model of end stage liver disease; [redacted]; NAFLD = nonalcoholic fatty liver disease; NFS = NAFLD fibrosis score; [redacted]; TEAE = treatment-emergent adverse event; [redacted]

13. ASSESSMENTS OF EFFICACY

13.1. Liver Biopsies

Given that historical biopsies are to be obtained no more than 6 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.

Liver biopsies will generally be obtained from the right lobe of the liver as described in a study specific histology manual. Liver biopsies are to be performed after the hepatobiliary ultrasound for [redacted]. If the initial biopsy was obtained from the left lobe, then subsequent biopsies must be obtained from the left lobe. Biopsies should be at least 2 cm in length. If a serial liver biopsy is required, the biopsy should not be performed within 6 months of a prior liver biopsy, unless clinically indicated. For subjects who develop potential liver-related clinical outcomes during the study, protocol-specified biopsies for study visits after onset of the potential outcome event may not be required.

The investigator will assess the clinical criteria for progression of fibrosis to cirrhosis for each subject during the study. If non-invasive indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy should be obtained and sent for central reading. Updated guidance on criteria to trigger an unscheduled liver biopsy in subjects with potential progression to cirrhosis may be provided to investigators separately.

If possible, a PK blood sample should be collected at the time of the liver biopsy.

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 biopsy assessments will be performed centrally, including assessments from biopsies to determine study eligibility and unscheduled biopsies, and biopsies that may be performed to confirm cirrhosis according to criteria described in Section 7.4.2.

To determine eligibility at enrollment, a central pathologist must confirm histological presence of NASH and a minimum NAS of 4 with a score of at least 1 in each component of NAS. For each biopsy, key features of NASH (ie, steatosis, lobular inflammation, and hepatocellular ballooning) and fibrosis staging will be graded in accordance with the NASH CRN criteria for scoring (Kleiner 2005) as summarized in Table 7.

Table 7: 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% 2 = >33% - 66% 3 = >66%	Stage 0	No Fibrosis
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, persinusoidal Moderate, zone 3, perisinusoidal Portal / periportal
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

In addition to the primary scoring system of NASH CRN, biopsy samples from the Month 18 Interim Analysis will also be scored based on modified Ishak scoring (Ishak 1995) and SAF scoring (Bedossa 2014) for all subjects as well as for quantitative collagen for a subset of subjects as exploratory assessments. Any extra biopsy tissue may undergo exploratory histological evaluations such as alpha-smooth muscle actin or bile acid transporter analysis.

13.2. Prospective Surveillance

[redacted] screening will include a hepatobiliary ultrasound and AFP assessment according to the schedule presented in Table 1. For subjects who develop [redacted] during the study, [redacted] screening assessments for study visits after onset of [redacted] are not required.

[redacted]

13.4. Efficacy Laboratory Assessments

Refer to Section 15.2.6 for instructions regarding sample collection and Table 12 for a full list of analytes to be tested.

[redacted]

13.7. Assessments for the Various Subsets of Subjects

At selected investigational sites, at least 300 subjects will have the option to provide blood samples for measurement of OCA PK concentrations.

At study sites in the United States, subjects will have the option to provide stool samples for microbiome/metabolome analysis only if they provided baseline (Day 1) samples.

PK and microbiome/metabolome assessments are optional, and subjects may decline to participate without affecting their involvement in the rest of the study.

At selected centers where the devices are available, subjects may participate in [redacted]. Biopsy samples will be scored for quantitative

collagen for a subset of subjects as described in Section 13.1.1. The schedule of assessments is presented in Table 1.

[redacted]

14. CLINICAL PHARMACOLOGY ASSESSMENTS

[redacted]

14.1.2. Subjects Who Develop Cirrhosis and Child-Pugh Class A

Subjects who develop cirrhosis and are Child-Pugh Class A (CP score <7) will have their dose adjusted (refer to Table 4). These subjects will provide 1 blood sample for PK assessment prior to dose adjustment, at the next scheduled visit. The PK assessment will measure serum concentrations of OCA, its conjugates (glyco-OCA and tauro-OCA), and OCA-glucuronide. The time of the last dose of investigational product and the time of the last meal will be recorded. The subject will then begin taking the adjusted dose of investigational product, thereafter, at the appropriate time.

14.1.2.1. Subjects Who Interrupt or Discontinue Investigational Product due to Cirrhosis or Hepatic Injury

Subjects who are considered to have potentially progressed to cirrhosis and discontinue investigational product due to progression to cirrhosis and due to Child Pugh score ≥7 or interrupt investigational product due to hepatic injury will provide a PK blood sample within ≤7 days from interruption or discontinuation of the investigational product (refer to Table 4).

15. ASSESSMENTS OF SAFETY

15.1. Adverse Events and Serious Adverse Events

15.1.1. Definition of Adverse Events

15.1.1.1. Adverse Event

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

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the 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 if they develop any of the signs and symptoms of intercurrent illness and/or potential adverse events listed in Appendix C.

15.1.1.2. Treatment-Emergent Adverse Event

A treatment-emergent AE (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.

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 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

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 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 will be recorded in the eCRF. If a PK sample cannot be collected within 7 days, the reason should be recorded in the eCRF.

15.1.2. 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.

15.1.3. 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," "possible" or "probable," 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.

15.1.4. 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.

15.1.5. 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 10, must be entered on the AE CRF. 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 current version of the CTCAE manual for guidance on appropriate grading.

Table 10: 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.

15.1.5.1. Severity of Pruritus (as an AE)

To ensure consistency in reporting, pruritus AEs must be graded for severity (ie, intensity) using the current version of the CTCAE (Appendix D) the category definitions are included in Table 11 for reference. As pruritus is a subjective symptom, clinical judgment should be used to determine its management.

Table 11: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus
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, the occurrence and magnitude of which are not readily measured objectively, 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. Guidance for the management of subjects experiencing significant pruritus are provided in Table 4 (Section 7.7) and includes:

- Pruritus ≥Grade 3 in severity: Discontinue investigational product
- Pruritus ≤Grade 2 in severity: One or more of the following may be considered:
  - Drug holiday or less frequent dosing at the discretion of the Investigator.
  - 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 9.3.

– Other medical therapies may be considered, as deemed clinically appropriate and based on current practice guidelines (EASL 2017) or literature (Hegade 2015).

15.1.6. Reporting of Adverse Events and Serious Adverse Events

15.1.6.1. 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 CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product. 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 promptly when any signs or symptoms of hepatic decompensation are observed in any subject.

15.1.6.2. Reporting of Serious Adverse Events

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

All SAEs must be reported to the Sponsor (including potential liver-related clinical outcome events that qualify as serious).

SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the event. In the event that the EDC system is inaccessible, an SAE may be reported by:

[redacted]

If an SAE is reported by 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 faxed to [redacted] or emailed to [redacted] as 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.

SAEs involving potential liver-related clinical outcome events will be processed and reported by the Sponsor as described in Section 15.1.7.

15.1.7. Potential 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, refer to Section 15.1.2 for definition of SUSAR.

Given that the liver-related clinical outcome events could also meet the criteria of a SUSAR, which would necessitate unblinding for expedited reporting, the Sponsor will not expeditiously report potential liver-related clinical outcome events in order to retain the study blind and preserve the integrity of the clinical outcomes endpoint. These events will be selected as a

"study event" on the Adverse Event CRF and will be submitted for adjudication to the Hepatic Outcomes Committee as described in Section 16.11.

The Sponsor will consider the following list of clinical outcome events (MedDRA preferred terms) to be disease related and exempt from expeditious regulatory reporting, but will continue to report them in a non-expeditious manner: death, end-stage liver disease (preferred term: chronic hepatic failure), liver transplant (preferred term: liver transplant), [redacted], variceal bleeding (preferred terms: gastroesophageal variceal haemorrhage, esophageal varices haemorrhage), hepatic encephalopathy (preferred term: hepatic encephalopathy), spontaneous bacterial peritonitis (preferred term: peritonitis bacterial), ascites secondary to cirrhosis (preferred term: ascites), and progression to cirrhosis (preferred term: hepatic cirrhosis).

15.1.8. Additional Investigator Responsibilities for SAEs

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

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

15.1.9. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study

Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 15.1.6.2.

15.1.10. 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 15.1.6.2.

All SAEs that occur within 30 days of discontinuation from the study, whether or not they are related to investigational product, should be reported to the Sponsor within 24 hours by following the instructions provided in Section 15.1.6.2.

15.1.11. 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 CRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

All subjects showing possible drug-induced liver injury 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 CRF. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be drug-induced liver injury, indicating that liver injury was related to underlying liver disease.

If a subject experiences symptoms consistent with cholelithiasis 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.

15.1.12. 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 (see Table 4) and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in the EDC system and downloading and completing the Pregnancy Report Form. The Pregnancy Report Form must be emailed to [redacted]. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor.

The subject may re-start investigational product when she is no longer pregnant or breastfeeding at the discretion of the Investigator and after discussion with the Medical Monitor. The subject must have a negative pregnancy test before restarting investigational product. If a subject's pregnancy is terminated early (planned or unplanned), she must have termination of the pregnancy confirmed by a serum β-hCG test before restarting investigational product.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 15.1.6 must also be followed.

15.2. Other Safety Parameters

15.2.1. 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, gender, race, and ethnicity) will be recorded.

15.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the visits specified in Table 1. 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 CRF page.

15.2.3. Vital Signs

Vital signs will be assessed at the visits specified in Table 1. Vital signs include body temperature, sitting heart rate, respiratory rate, and sitting blood pressure. When taking heart rate, respiratory rate, and blood pressure readings, subjects should be seated quietly for a minimum of 3 minutes before the readings are taken.

15.2.4. Electrocardiogram

Standard 12-lead ECGs will be collected at the visits specified in Table 1. 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 CRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormality on ECGs should be reported on the AE CRF 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.

15.2.5. 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 using the AUDIT, smoking habits, and caffeine consumption CRFs. AUDIT is a 10-item questionnaire that uses the domains of alcohol consumption, drinking behavior, and alcohol-related problems (Saunders 1993)

15.2.6. Laboratory Assessments

Except for Screening and safety lab visits between regularly scheduled visits, 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 CRF. If the subject reports having eaten (water is permitted) within 8 hours, the Investigator or designee will document accordingly in the source

and CRF and remind the subject that fasting is required before all regularly scheduled study visits after screening (exception – safety lab visits).

Blood, urine, and stool samples for laboratory assessments will be collected at the visits specified in Table 1. Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample processing, labeling, and shipping will be provided in separate procedural manuals. All necessary collection supplies will be provided by the appropriate 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 list of laboratory analytes to be tested is shown in Table 12.

Table 12: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
All Subjects	
Serum chemistry	Albumin, BUN, direct bilirubin (ie, conjugated bilirubin), indirect bilirubin total bilirubin, AST, ALT, ALP, GGT, creatinine, electrolytes (calcium, chloride, magnesium, phosphorus, potassium, sodium), total protein, bicarbonate, free fatty acids (only at visits that specify analysis of this analyte), creatine phosphokinase (only at visits that specify analysis of this analyte), LDL, HDL, VLDL, total cholesterol, triglycerides, and calculation of eGFR
Hematology	Hemoglobin, hematocrit, white blood count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets, red blood cell count (including MCV, MCH, MCHC)
[redacted]	
Urinalysis	pH, specific gravity, total protein, glucose, ketones, bilirubin, blood, microscopic exam, urobilinogen, albumin, creatinine, leucocytes, nitrates, albumin/creatinine ratio (if positive)
[redacted]	

Table 12: List of Laboratory Analytes to be Tested (Continued)

Laboratory Assessment	Analyte
Virology	HbsAg, HCV
Pregnancy Test (female subjects of childbearing potential)	β-hCG
For the Various Subsets of Subjects	
[redacted]	
Microbiome/Metabolome Analysis	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

AFP = alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; [redacted] BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; [redacted] DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; [redacted] GGT = gamma-glutamyl transferase; [redacted]; HbA1c = hemoglobin A1c; HbsAg = hepatitis B surface antigen; [redacted]; HCV = hepatitis C virus; HDL – high-density lipoprotein; [redacted] 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; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; NFS = NAFLD fibrosis score; PAI-1 = plasminogen activator inhibitor-1; [redacted]; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; TNF-α = tumor necrosis factor—α; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein

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 9.3.3 and Appendix A).

Urine-based β-hCG pregnancy tests will be performed for female subjects of childbearing potential at the visits specified in Table 1. 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 15.1.12 through pregnancy outcome.

International normalized ratio (INR) will be calculated based on prothrombin time value by the central laboratory. 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. 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.

16. STATISTICS

A 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 before study database lock.

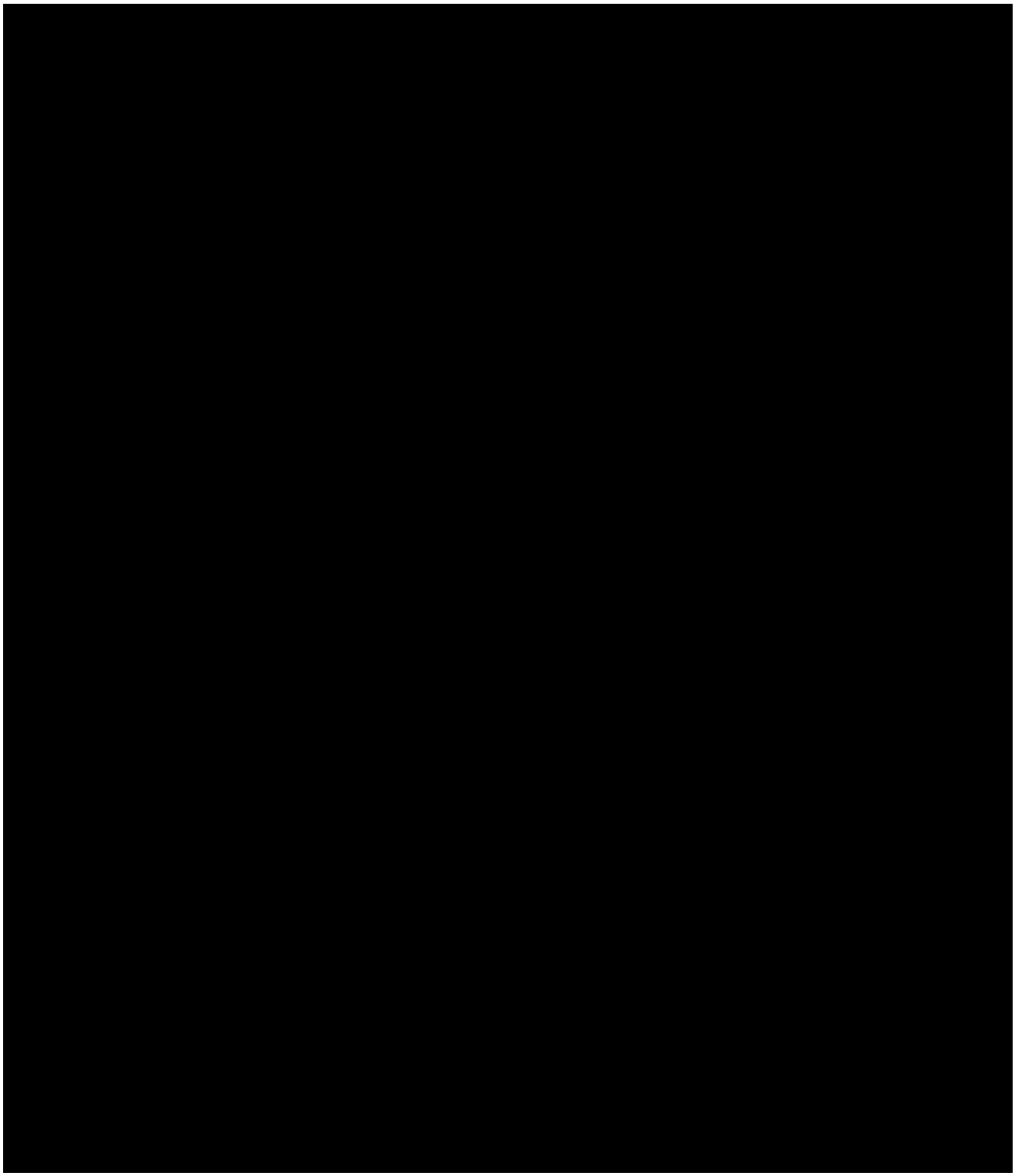
Data flow, access, process and disclosure will be described in a DAP. The DAP will cover the process by which an independent statistical group will conduct analyses, including the Month 18 Interim Analyses to support regulatory filing for conditional marketing approval.

16.1. Primary Analysis Populations (For End-of-Study Analysis)

The following subject populations will be evaluated and used for presentation and analysis of the data:

- The Intent-to-Treat (ITT) Population will include all randomized subjects with fibrosis stage 2 or stage 3 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.
- The Full Analysis Population will include all randomized subjects, all fibrosis stages, who receive at least 1 dose of investigational product (OCA or placebo). Treatment assignment will be based on the randomized treatment.
- 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 Safety Population will include all randomized subjects, all fibrosis stages, 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 include all OCA subjects who have at least 1 confirmed fasted analyzable sample. Subjects must have been fasting for approximately 8 hours before the visit and must not have any major protocol deviations that potentially affect exposure levels. The PK Population will be used for OCA PK and PK/PD analyses.

Additional details regarding the cutoff for the Month 18 Interim Analysis population will be defined in the SAP.



16.3. Efficacy Analysis at Month 18 Interim Analysis

16.3.1. Primary Efficacy Analysis

All efficacy analysis will be conducted using the ITT population (only including fibrosis stage 2 and stage 3 subjects). The hypothesis testing of primary and (key) secondary endpoints will be conducted with control of Type 1 error (OCA 25 mg, then 10 mg). The 2-sided alpha allocated to all testing in this single study will be 0.05. The histological endpoints will be tested at the Month 18 Interim Analysis with an alpha level of 0.02. The primary clinical outcomes endpoint will be tested with a minimum alpha level of 0.03, and this may be augmented by recycled alpha from the Month 18 Interim Analysis. Adjustments for multiplicity are specified in Section 16.7, and additional details on the testing will be provided in the SAP.

The primary endpoints at the Month 18 Interim Analysis are:

- Improvement in fibrosis by 1 stage or more, with no worsening of hepatocellular ballooning, no worsening of lobular inflammation and no worsening of steatosis
- NASH resolution with no worsening of fibrosis

The primary efficacy analysis for fibrosis improvement at the Month 18 Interim Analysis will test the following hypotheses using the ITT population (the ITT population for the Month 18 Interim Analysis is not the same as that for the overall study and is defined in the SAP):

- H_{01}: The percentage of subjects with fibrosis improvement by 1 stage or more, no worsening of hepatocellular ballooning, and no worsening lobular inflammation is equal between placebo and OCA.
- H_{11}: The percentage of subjects with fibrosis improvement by 1 stage or more, no worsening of hepatocellular ballooning, and no worsening lobular inflammation is different between placebo and OCA.

The primary efficacy analysis for the resolution of NASH with no worsening of fibrosis at Month 18 Interim Analysis will test the following hypotheses using the ITT population:

- H_{02}: The percentage of subjects with NASH resolution and no worsening of fibrosis is equal between placebo and OCA.
- H_{12}: The percentage of subjects with NASH resolution and no worsening of fibrosis is different between placebo and OCA.

NASH resolution is defined as the 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. The primary efficacy analyses at the Month 18 Interim Analysis will compare placebo and OCA using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata (type 2 diabetes at enrollment [yes/no] and use of TZDs/glitazones or vitamin E at baseline [yes/no]).

Supportive analyses will be conducted using PP population and all fibrosis stages (Full Analysis Population). Additional supportive and sensitivity analyses along with analysis populations of interest will be defined in the SAP.

16.3.2. Secondary Efficacy Analyses

16.3.2.1. Histology Analysis

Secondary efficacy endpoints at the Month 18 Interim Analysis are:

- Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
- No worsening of fibrosis AND no worsening of NASH
- Percentage of subjects with improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning).
- Percentage of subjects with improvement of fibrosis by at least 2 stages
- Percentage of subjects with improvement in NAS by at least 2 points with no worsening of fibrosis
- Improvement of fibrosis and resolution of NASH as a composite and as defined by both endpoints being met in the same subject
- Histological progression to cirrhosis
- Resolution of fibrosis

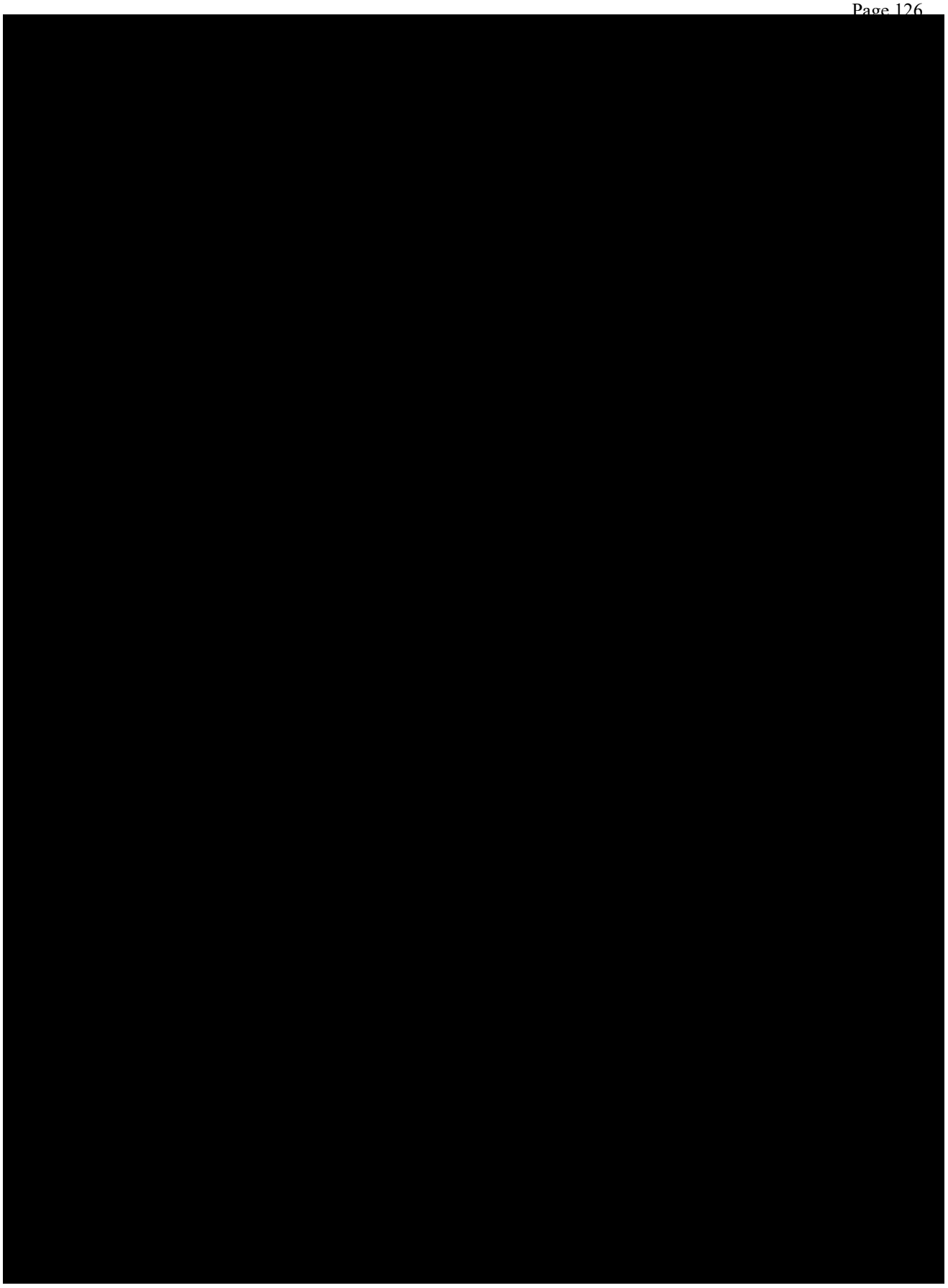
16.3.2.2. Liver Biochemistry and Liver Function

The following laboratory parameters will be summarized by treatment group: ALT, AST, gamma-glutamyl transferase (GGT), ALP, total and direct bilirubin, albumin, INR, and platelets.

Analyses of change from baseline and percent change from baseline will be performed as specified in the SAP.

Descriptive statistics of the laboratory values will be summarized by treatment group and visit. The results, change from baseline, and percentage change from baseline values as well as estimates of least-square (LS) means, standard errors, and 95% confidence intervals (CIs) will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the standard error of the difference, and 95% CI of the difference will be presented. Baseline is defined as the mean of all available evaluations before treatment.

[redacted]



16.4. Efficacy Analyses at End of Study

16.4.1. Primary Efficacy Analysis

All efficacy analysis at EOS will be conducted using the ITT population (only including fibrosis stage 2 and 3 subjects). The hypothesis testing of primary and (key) secondary endpoints will be conducted in with control of Type 1 error (OCA 25 mg, then 10 mg). Adjustments for multiplicity are specified in Section 16.7 and additional details on the testing at EOS will be provided in the SAP.

The primary efficacy endpoint at the EOS will be the time to first occurrence of one of the following post-randomization:

- Death (all-cause)
- MELD score ≥15
- Liver transplant
- Hospitalization (as defined by a stay of 24 hours or greater) 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)
- Progression to cirrhosis

The primary efficacy analysis for clinical outcomes at EOS will test the following hypothesis:

- H_{01}: The time to first occurrence of any of the adjudicated events for all-cause mortality and liver-related clinical outcomes are equal between placebo and OCA.
- H_{11}: The time to first occurrence of any of the adjudicated events for all-cause mortality and liver-related clinical outcomes are different between placebo and OCA.

Only adjudicated events (including progression to cirrhosis) will be included in analyses. Placebo and each OCA dose will be compared separately using a log rank test stratified by the randomization stratification factor. Kaplan-Meier (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.

16.4.2. Secondary Efficacy Analyses

16.4.2.1. Histology Analysis

- Improvement in fibrosis by 1 stage or more, with no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis
- NASH resolution with no worsening of fibrosis
- Improvement of fibrosis by at least 1 stage AND/OR resolution of NASH, without worsening of either
- No worsening of fibrosis AND no worsening of NASH
- Percentage of subjects with improvement in each key histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning).
- Percentage of subjects with improvement of fibrosis by at least 2 stages
- Percentage of subjects with improvement in NAS by at least 2 points with no worsening of fibrosis
- Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
- Resolution of fibrosis

16.4.2.2. Liver Biochemistry and Liver Function

The following laboratory parameters will be summarized by treatment group: ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets.

Analyses of change from baseline and percent change from baseline will be performed as specified in the SAP.

Descriptive statistics of the laboratory values will be summarized by treatment group and visit. The results, change from baseline, and percentage change from baseline values as well as estimates of least-square (LS) means, standard errors, and 95% Cis, will be presented by treatment group. Estimates of the mean difference between each active treatment group and placebo group, the standard error of the difference, and 95% CI of the difference will be presented. Baseline is defined as the mean of all available evaluations before treatment.

Each active OCA treatment group will be compared to placebo using the 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. 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. Subjects without any documentation of events will be censored at the date of last contact.

16.5. Interim Analyses Post Month 18 Interim Analysis

There will be 2 planned interim analyses to be conducted using group sequential approach in accordance to the SAP and DMC Charter at the accumulation of 50% and 80% of the total planned 291 adjudicated clinical outcome events. The primary efficacy endpoint for these planned interim analyses will be the clinical outcomes composite endpoint.

If either of these 2 Interim Analysis are significant, then all analyses described in Section 16.4 will be carried out.

16.6. 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.

16.6.1. Time to Event Endpoints

For the time-to-event analyses, including the primary clinical outcomes composite endpoint, only adjudicated events (including biopsy confirmed progression to cirrhosis) will be included. Subjects who do not experience an adjudicated event will be censored at the time of their last contact. Sensitivity analyses will be described in the SAP.

16.6.2. Quantitative Endpoints

For other efficacy endpoints utilizing an ANCOVA model, mixed-effect repeated measures model or the Wilcoxon Rank Sum Test, observed cases will serve as the primary analysis.

16.6.3. Responder Endpoints

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 any assessment at the specified timepoint and after baseline 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. Subjects who early terminate before Month 18, biopsy results at the time of early termination, if available, will be included in Month 18 histological endpoints analyses.

A completer analysis will also be conducted, 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.

Additional sensitivity analysis will be described in the SAP.

16.7. Multiple Comparisons/Multiplicity

The 2-sided alpha allocated to all testing in this single study will be 0.05. The histological endpoints will be tested at the Month 18 Interim Analysis with alpha level of 0.02. The primary clinical outcomes endpoint will be tested with a minimum alpha level of 0.03, which may be augmented by recycled alpha from the Month 18 Interim Analysis. Further details are provided in the SAP.

16.7.1. Multiplicity Adjustment for the Month 18 Interim Analysis

For the Month 18 Interim Analysis, testing methods to control overall Type 1 error will be implemented. The sequential testing order will be: primary endpoints in 25 mg versus placebo, followed by primary endpoints in 10 mg versus placebo; details will be provided in the SAP.

16.7.2. Multiplicity Adjustment for Interim (Post Month 18 Interim Analysis) and EOS Analyses

For the interim and EOS analyses of the primary and (key) secondary endpoints, OCA will be compared to placebo. O'Brien-Fleming type alpha-spending function will be used to control overall alpha level allocated for clinical outcomes for DMC analysis at 50% and 80% information fraction and at EOS.

The SAP will specify the methods and alpha levels for the interim analyses and EOS final analysis. The DMC will review the interim criterion for efficacy in conjunction with detailed safety data and other relevant information to determine whether to continue the study.

16.8. Examination of Subgroups

Both at the interim and final analyses, 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).

Key subgroups of interest are fibrosis stage and diabetes status. Additional parameters for subgroup analyses include, but are not limited to: age, sex, race, BMI, NAS, ballooning, FRS, statin or antihypertensive medication use, ALT, AST, GGT, and geographic region. Further details regarding subgroups analyses will be specified in the SAP.

16.9. Safety Analysis

Safety data, including AEs and clinical laboratory observations, will be summarized by treatment group using the Safety Population. The evaluation of safety data will be conducted at both the interim and final analyses.

16.9.1. Adverse Events

AEs will be coded using the Medical Dictionary of 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.

16.9.2. Hepatic and Renal Safety Adjudication

Potential events of hepatic injury and AKI will be adjudicated during the study (Section 16.11). The adjudication of the events of hepatic injury will be separate from the adjudication of events for assessment of the primary outcomes endpoint 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.

16.9.3. Cardiovascular Event 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 (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (See

Section 16.11). Undetermined cause of death will be classified as a cardiovascular death by the CAC.

There will be no formal hypothesis testing of MACE at the Month 18 Interim Analysis. The EOS assessment of MACE will include all MACE events occurred from the start of the study.

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 the 2 dose levels of 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.

16.9.4. Cardiovascular Risk Assessments

Cardiovascular risk scores will be calculated for assessments including:

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

Each score is derived from a subject's age, sex, smoking status, total cholesterol and HDL levels, systolic 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 each on-study evaluation. The change and percentage change from Baseline will also be summarized. Baseline is defined as the last assessment before treatment. Further analysis details will be specified in the SAP.

16.9.5. Clinical Laboratory Evaluations

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.

16.9.6. Lipoprotein Evaluations

Lipoprotein samples, separate from the serum chemistry samples, collected for a subset of subjects up to Version 7 of the protocol, will be assayed in addition to serum lipid analyses performed as part of the serum chemistry panel. 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.

16.9.7. Additional Safety Analysis

16.9.7.1. Vital Signs

The results and change from Baseline to each on-study evaluation visit will be summarized for body temperature, sitting heart rate, and respiratory rate. Baseline is defined as the mean of all available evaluations before treatment.

16.9.7.2. Electrocardiograms

The ECG data analysis will be conducted based on methodology recommended in the ICH E14 guideline, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs.

Baseline is defined as the mean of all available evaluations before treatment. Descriptive statistics of ECG parameters (time between 2 consecutive R waves [RR], PR, QRS, QT, and QT interval corrected by the 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 subjects with values of >450 msec, >480 msec, and >500 msec will be presented, and the number of subjects 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.

16.10. Data Monitoring Committee

An independent DMC that includes 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. 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 Food and Drug Administration (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 meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data as well as the adjudication assessments from the 4 adjudication committees listed in Section 16.11. 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 potential 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.

Data flow, access, process and disclosure will be described in a DAP. The DAP will cover the process by which an independent statistical group will conduct analyses and provide to the DMC, including the Month 18 Interim Analyses to support regulatory filing for conditional marketing approval.

16.11. Adjudication Committees

All potential liver-related clinical outcomes and potential events of hepatic injury, AKI, MACE, 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:

- CAC: 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 including clinical events and histological findings of potential disease progression to cirrhosis
- 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.

Specific details of the events that will be adjudicated by the CAC, 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 outside of a protocol amendment.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DMC members, or consultants. Any candidate found to have a conflict or whose name is listed on the FDA debarment list 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.

Histological progression to cirrhosis will be determined by central reading of liver biopsies. A biopsy evaluation form signed by one of the study-specific central pathologists will be necessary to confirm histological progression to cirrhosis. Clinical events and histological findings of potential disease progression to cirrhosis will be adjudicated by the Hepatic Outcomes Committee. The end of study primary efficacy endpoints of clinical composite outcome events are described in Section 16.4.1.

17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

17.1. Study Monitoring

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

In order to perform this role, the CRA must perform source data verification and as such must be given access to the subject’s primary source documentation (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 CRF. The CRF 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.

17.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IRB/IEC and/or a regulatory agency to conduct one or more site audits during or after the study and agrees to

allow access to all study related documentation and information and be available for discussion about the study.

17.3. Documentation Associated with Interim Data

To ensure continued unbiased conduct during the study and unbiased analysis at the end of the study, a select group of unblinded personnel will be identified and charged with producing the associated unblinded documents to support regulatory submissions for conditional marketing approval. All other personnel, including those charged with completing the study, will remain blinded to individual subject treatment assignments and unblinded aggregated data as described in the DAP.

18. QUALITY CONTROL AND QUALITY ASSURANCE

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

Training sessions, regular monitoring of the 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 17.2 for more details regarding the audit process.

19. ETHICS

19.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to the Sponsor 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 ethics committee for review.

The Investigator is responsible for informing the IRB/IEC of any revisions to the protocol in accordance with local requirements. A favorable opinion on revisions will be obtained before implementation, unless the revisions are 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 or IEC upon receipt of revisions 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. The Sponsor will provide this information to the Investigator.

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

19.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

19.3. 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 risk 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 ICF(s) must be obtained before conducting any study procedures.

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

19.4. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (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 reports and communications relating to subjects in this study that are disclosed to an authorized third party will identify subjects only by protocol and assigned number and will be shared in a secure manner. All data shall be secured against unauthorized access.

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

The written information sheet 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 their disclosure to unauthorized third parties. The pertinent sections of the data protection laws in which the country is being conducted will be complied with in full.

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

20. INVESTIGATOR OBLIGATIONS

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

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

20.1. AE Reporting

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

20.2. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee). Only the Sponsor may revise 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 revision 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.

20.3. Regulatory Documentation

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

- Approved ICF (all versions)
- IRB/IEC approvals (of protocol/subsequent revisions, subject questionnaires, etc)
- Form FDA 1572
- Current medical license
- Curriculum vitae
- Laboratory certification and reference ranges
- Financial disclosure forms

20.4. Ethics Review (IRB or IEC)

Please see Section 19.1 for the Investigator's responsibilities regarding ethics review.

20.5. Archiving and Record Retention

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

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

21. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). 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 Study Registries (eg, clinicaltrials.gov): 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 (when available) 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 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 before 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 before 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: The Sponsor, 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 before submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies, or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, eg, protocol and subsequent revisions, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

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APPENDIX A. MANAGEMENT OF CHANGES IN CHOLESTEROL

In previous studies evaluating obeticholic acid (OCA) for nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), changes in lipid profile were observed in response to OCA therapy. As described in the Investigator's Brochure, data from these studies suggest that any OCA-induced increase in low-density lipoprotein (LDL) cholesterol can be managed by statins. While there are no long term data with OCA in NASH to assess any long-term increase in cardiovascular risks, given the increased cardiovascular mortality in NASH patients in general, it is important to monitor for changes in cholesterol levels, and manage LDL levels in the context of other risk factors.

Statins are sometimes reluctantly used by healthcare professionals in patients with NAFLD or NASH, which may in part be due to the contraindication in statin package inserts for use in patients with active liver disease. There is growing evidence of the safety of statins in patients with elevated baseline liver enzymes, including in subjects with compensated NAFLD/NASH. During the conduct of Study 747-303, routine study visits provide an opportunity to detect any adverse effects that may arise due to blinded or open-label study drug or concomitant medication use such as statins through various assessments of the liver. Liver enzyme elevations are usually reversible with continued use or after discontinuing treatment without evidence of long-term injury.

The purpose of this guidance document is to provide participating Investigators a uniform approach for monitoring LDL concentrations and considering treatment of LDL cholesterol increases during the study. The Investigator may consider alternate cholesterol management strategies on a case-by-case basis. This guidance summarizes recommendations for the management of LDL cholesterol based on the 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).

Investigators should closely monitor subjects' LDL concentrations and evaluate each subject with respect to:

- Magnitude of LDL increase (ie, absolute LDL value in the context of individual cardiovascular risk profile)
- Cardiovascular risk factors
- Risk-benefit assessment of statin or other appropriate dyslipidemia therapy
- Any other factors that are relevant to dyslipidemia management

Recommended LDL Management Algorithm (Figure A1):

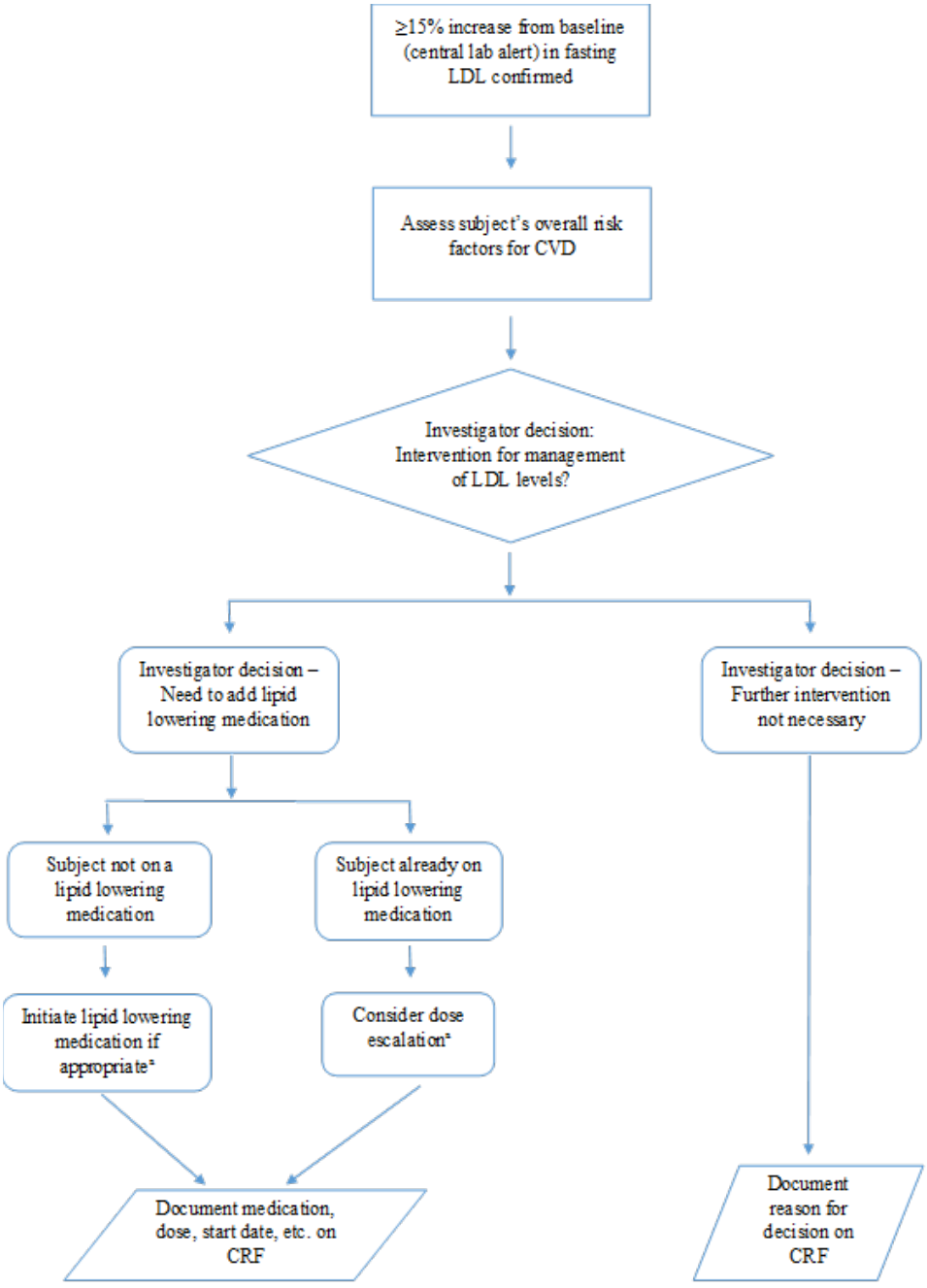
- Investigators and/or study staff will be alerted by the central laboratory when a ≥15% increase from baseline is detected in a subject's LDL concentration as part of the standard lab panel conducted at every study visit.
  - If an LDL value is elevated and the subject reports having eaten within 8 hours before the blood draw, the Investigator may repeat the assessment under fasting conditions to better assess the magnitude of the increase.

- If the LDL cholesterol increase of ≥15% relative to study baseline is confirmed, Investigators should also assess any other cardiovascular disease risk factors that may be present. A subject may be considered at high risk for cardiovascular disease if any of the following factors are present:
  - History of atherosclerotic cardiovascular disease (eg, prior myocardial infarction, angina) or cerebrovascular disease
  - High LDL and/or low high-density lipoprotein values
  - Age >50
  - Diabetes mellitus
  - Hypertension
  - Tobacco smoker
  - Male gender
- If the Investigator determines that intervention is warranted after a risk-benefit analysis for statin versus non-statin dyslipidemia therapy, the Investigator may:
  - Initiate statins at an appropriate dose (high-, moderate-, or low-intensity statin depending on the subject's cardiovascular risk profile) in subjects who are not currently taking a statin
  - Up-titrate statin dose in subjects who are already taking a statin at less than maximum (or maximum tolerated) dose or switch to a more potent statin in subjects taking maximum dose of a low or moderate intensity statin
  - Initiate or up-titrate non-statin dyslipidemia therapy in subjects for whom statin use is not preferred or are already on a maximum (or maximum tolerated) statin therapy (eg, ezetimibe, fibrates, PCSK9 inhibitors, and bile acid sequestrants [see protocol for instructions regarding dosing of investigational product and bile acid sequestrants])
- If any dyslipidemia therapy is initiated or up-titrated:
  - The new concomitant medication or change in dose must be documented on the case report form (CRF);
  - Dyslipidemia therapy initiation or dose adjustments may be considered appropriate to achieve LDL concentrations at or below baseline
  - If treatment with statins is initiated, women of childbearing potential must be informed that statin use is contraindicated during pregnancy. Methods of contraception should be reviewed and modified if necessary to ensure highly effective methods with failure rates <1% per year, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or history of vasectomy of partner are used.

- If the Investigator determines that intervention is not necessary, based on LDL evaluation and assessment of other risk factors, this decision and the reason for the decision must be documented on the CRF.

This guidance may be updated over the course of the study as cardiovascular disease prevention guidelines evolve over time. New lipid findings as a result of ongoing evaluations will be included in the Investigator's Brochure during periodic updates.

Figure A1: LDL Management Flow Chart

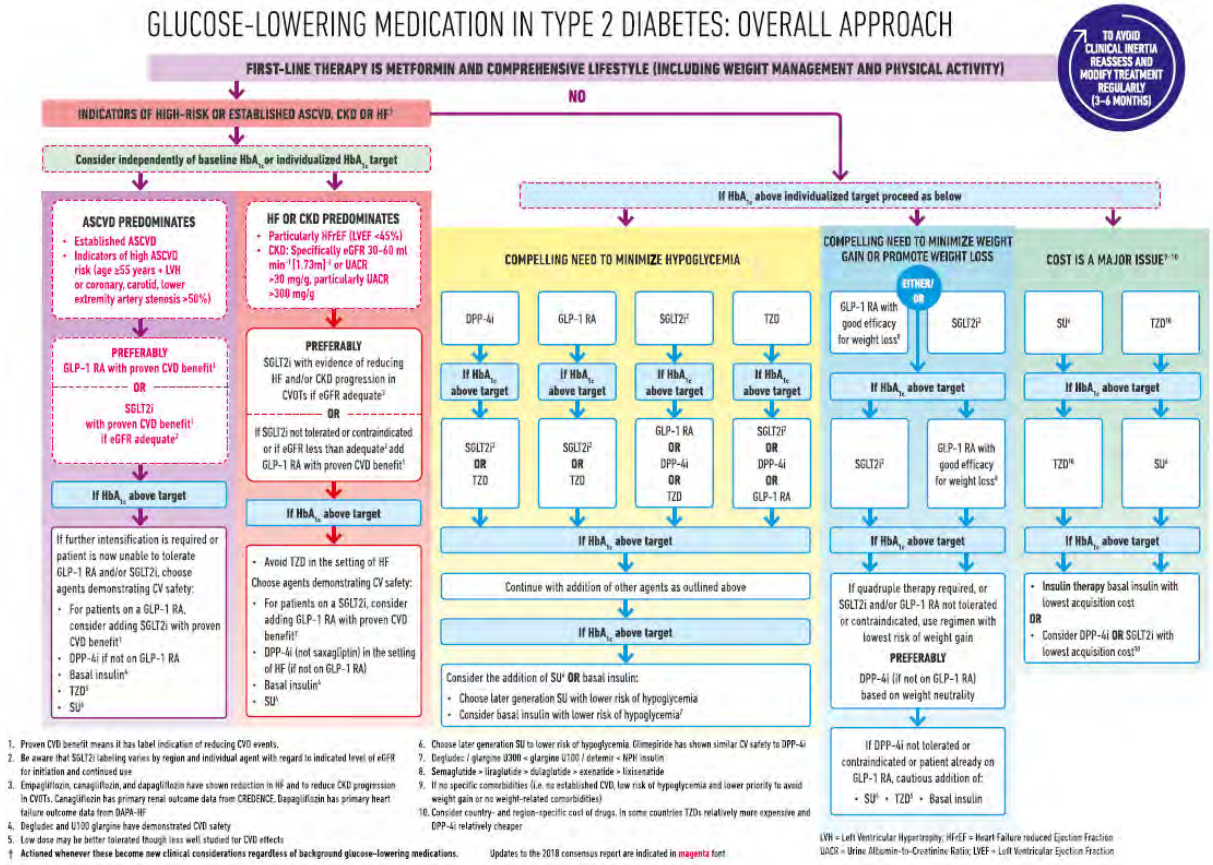


[a] If a subject is unable to tolerate statins other lipid-lowering modalities may be considered and must be documented, including reason for choice of medication.

APPENDIX B. MANAGEMENT OF HYPERGLYCEMIA

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

Figure B2: 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 Section 7.5.1) • Significant upper abdominal pain with nausea, vomiting, or fever, jaundice
Hyperglycemia **(Protocol Section 9.3.4)**	• 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: a. Death witnessed and occurring without new or worsening symptoms b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI c. 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) d. Death after unsuccessful resuscitation from cardiac arrest (eg, implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest) e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology f. 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 Chapter 1, Section 6, and Chapter 6)	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
• 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 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

Event	Definitions
	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 – 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:

Event	Definitions
	– 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: 1. 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 2. 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 3. 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). • And believed to be responsible for the myocardial ischemic symptoms/signs.

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td></td><td>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>
<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>
</table>

Event	Definitions
Heart Failure (A HF event includes hospitalization for HF and may include urgent outpatient visits)	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 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

Event	Definitions
	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 (ie, 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 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.

Event	Definitions
	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 (CFR), or fractional flow reserve (FFR), insertion of a guide wire will NOT be considered PCI.

Event	Definitions
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.

<table>
<tr><th>Event</th><th>Definitions</th></tr>
<tr><td>Target Vessel Revascularization (TVR):</td><td>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.</td></tr>
<tr><td>Vascular Complications:</td><td>• 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.
• 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>
</table>
</td></tr>
</table>

Event	Definitions	
	Mid right coronary artery	Middle portion of the right coronary artery, from the origin of the first right ventricular branch to the acute margin (mRCA)
	Distal right coronary artery	Distal portion of the right coronary artery, from the acute margin to the origin of the posterior descending artery (dRCA)
	Right posterior descending artery	In right dominant and mixed circulations, the vessel that runs in the posterior interventricular groove and supplies septal perforator branches (PDA)
	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 bifucation (LM)
	Left main coronary artery bifucation	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)

Event	Definitions	
	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 desending artery to supply the anterolateral wall of the left ventricle (D1)
	First diagonal lateral branch	Branch of the first diagonal branch
	Second diagonal branch	Second of the three longest branches originating from the left anterior desending 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 desending 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)

Event	Definitions	
	First obtuse marginal branch	First of the three longest branches originating from the left circumflex artery to supply the laterall 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 laterall 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 laterall wall of the left ventricle (OM3)
	Third obtuse marginal lateral branch	Branch of the third marginal branch
	Left atrioventricular artery	In left dominant and mixed circulations, the distal continuation of the left circumflex coronary artery in the posterior atrioventricular groove
	Left posterior descending artery	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)
	First left posterolateral branch	In left dominant and mixed circulations, the first posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL1)
	Second left posterolateral branch	In left dominant and mixed circulations, the second posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL2)
	Third left posterolateral branch	In left dominant and mixed circulations, the third posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL3)
	Ramus intermedius branch	Branch vessel whose origin bisects the origins of the left anterior descending and circumflex arteries (RI)
	Ramus intermedius lateral branch	Branch of the ramus intermedius branch

Event	Definitions
Dissection:	**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
Late Loss:	Minimum lumen diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the index procedure. MLDs are measured by QCA.
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.

Event	Definitions
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 • 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.

Event	Definitions
	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 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).

Event	Definitions
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 lesion revascularization occurs in the absence of protocol-directed surveillance ultrasound or angiography.
Vessel Patency:	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.

<table>
<tr><th>Event</th><th>Definitions</th></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
– Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)</td></tr>
</table>

Event	Definitions
	– 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 days[g] 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: PROTOCOL 747-303 VERSION 11.0 (DATED 04 MAY 2021)

Protocol 747-303 was revised to include the following information:

1) Update to the end-of-study primary objective for progression of cirrhosis to include all clinical evidence beyond only histological changes
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 due to suspected hepatic injury and progression to cirrhosis, within 7 days of experiencing a serious adverse event, and at the time of liver biopsy. Additional PK sparse sample collection was added to each study visit after Month 18 to adequately capture the OCA exposure-response relationships for efficacy and safety
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 to each study visit after Month 18.
6) Inclusion of local laboratory results and reference ranges into the eCRF and inclusion local pathology reports 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) Study duration was updated from 7 to 10 years based on current estimates for outcome accrual
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 10.0 is crossed out and revised text in Version 11.0 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 11.0 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 10.0, 03 Feb 2020)	Revised Text (Version 11.0, 04 May 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]~~, PhD~~ [redacted], Clinical Development Intercept Pharmaceuticals, Inc.	[redacted]**, MD** [redacted], Clinical Development Intercept Pharmaceuticals, Inc.	Sponsor wet signature approver updated to reflect change in personnel
Study Personnel Contact Information	Primary Contact: [redacted], MD ~~Lead Medical Monitor/Medical Expert~~ ~~PRA Health Sciences~~ Secondary Contact: [redacted]~~, PharmD, MS~~ [redacted] Intercept Pharmaceuticals, Inc. Email: [redacted]	Primary Contact: **PRA Health Sciences Medical Monitor Team** [redacted]**, MD** [redacted]**, MD** [redacted], MD **(Lead)** Secondary Contact: [redacted]**, M.D.** [redacted] Intercept Pharmaceuticals, Inc. Email: [redacted] **Telephone** [redacted]	Primary contact information expanded to include the entire PRA medical monitor team Secondary contact was updated to reflect change in personnel
Section 5.3	Study 747-209 ~~is~~ further ~~evaluating~~ the effect of OCA and atorvastatin treatment on LDL metabolism in subjects with NASH to better understand the lipid profile changes observed in the FLINT study. Subjects with biopsy-confirmed NASH and fibrosis received placebo or OCA 5mg, 10 mg, or 25 mg once daily, for up to 4 weeks.	Study 747-209 further **evaluated** the effect of OCA and atorvastatin treatment on LDL metabolism in subjects with NASH to better understand the lipid profile changes observed in the FLINT study. Subjects with biopsy-confirmed NASH and fibrosis received placebo or OCA 5mg, 10 mg, or 25 mg once daily, for up to 4 weeks.	Updated language to reflect completion of Study 747-209

Section	Original Text (Version 10.0, 03 Feb 2020)	Revised Text (Version 11.0, 04 May 2021)	Key Change Reasons/ Justification for Change
Section 5.4 and 22	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 can improve steatohepatitis and resulting fibrosis, potentially delaying liver transplant or death.	The incidence of NASH is increasing and NASH **has become one of** the leading causes of liver transplant **(Wong 2020, Younossi 2020)**, highlighting the need for development of effective therapies that can improve steatohepatitis and resulting 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 the United States. Clin Gastroenterol Hepatol. 2020 Jun 9.**	Updated the language and references to provide support for statement regarding current rate of liver transplantation
Section 5.5	The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk. Recent safety findings in NASH clinical trials include ~~2~~ cases of hepatic decompensation reported as SUSARs, 1 of which resulted in death. ~~One case was reported in a subject with no evidence of cirrhosis at baseline; the subject's treatment assignment remains blinded.~~ The ~~second (fatal)~~ case was reported in a subject with cirrhosis and hepatic impairment at baseline; the subject was in the OCA 25 mg	The rate of progression and risk of decompensation is variable and may be rapid in certain patients, necessitating closer surveillance of patients at risk. Recent safety findings in NASH clinical trials include **9** cases of hepatic decompensation 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 an SAE of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.** The fatal case was reported in a subject	Known potential risks with investigational product and DMC recommendations were updated to reflect the language in the current version of the OCA Investigational Brochure (V19 27Mar2020)

Section	Original Text (Version 10.0, 03 Feb 2020)	Revised Text (Version 11.0, 04 May 2021)	Key Change Reasons/ Justification for Change
	treatment group. ~~Both cases involved numerous confounding factors that make evaluation of association with treatment difficult~~. Key liver-related findings: • eDISH analyses show no evidence of hepatic injury with OCA compared to placebo. • In PBC, hepatic AEs evaluated by Standardized MedDRA criteria showed a rate of hepatic AEs higher in OCA-treated subjects compared with those treated with placebo. • 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 Classification. While 1.5- and 1.7-fold increases in liver concentrations of OCA are predicted for subjects with Child-Pugh Class B and C, respectively, liver concentrations of OCA in subjects with Child-Pugh A are predicted to be similar to those of healthy control subjects (1.1-fold increase). • Serious liver-related adverse reactions have been reported in postmarketing in PBC patients with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Ocaliva was dosed more frequently than the recommended starting dosage of 5 mg once weekly. ~~Changes in lipid profiles have also been observed with OCA dosing, including an increase in low density lipoprotein (LDL) cholesterol and a~~	with cirrhosis and hepatic impairment at baseline; the subject was in the OCA 25 mg treatment group. Key liver-related findings: • eDISH analyses show no evidence of hepatic injury with OCA compared to placebo. • In PBC, hepatic AEs evaluated by Standardized MedDRA criteria showed a rate of hepatic AEs higher in OCA-treated subjects compared with those treated with placebo. **In NASH clinical trials, the incidence of hepatic TEAEs was similar between OCA and placebo groups. Serious hepatic TEAEs, however, occurred more frequently with OCA 25 mg, as compared to OCA 10 mg and placebo** • 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 Classification. While 1.5- and 1.7-fold increases in liver concentrations of OCA are predicted for subjects with Child-Pugh Class B and C, respectively, liver concentrations of OCA in subjects with Child-Pugh A are predicted to be similar to those of healthy control subjects (1.1-fold increase). **In a hepatic impairment study in NASH subjects with compensated 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**	

Section	Original Text (Version 10.0, 03 Feb 2020)	Revised Text (Version 11.0, 04 May 2021)	Key Change Reasons/ Justification for Change
	~~decrease in high-density lipoprotein (HDL) cholesterol. The clinical significance of these lipid findings remains unclear and is being studied further.~~ 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, 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.	**with decompensated cirrhosis (Child-Pugh Class B and Child-Pugh Class C).** • Serious liver-related adverse reactions have been reported in postmarketing in PBC patients with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Ocaliva was dosed more frequently than the recommended starting dosage of 5 mg once weekly. **OCA-related changes in serum lipids (decrease in high-density lipoprotein cholesterol [HDLc] and increase in LDLc) have been observed in healthy volunteers, in subjects with PBC and NASH, and in subjects with other underlying conditions. However, the pattern and magnitude, as well as the clinical significance of these changes, are not well understood and clearly depend on a subject's underlying condition and other comorbidities. Although increases in LDLc have generally been considered to be associated with increased cardiovascular risk, it is not possible to draw conclusions regarding the cardiovascular effect of OCA-related changes in lipid profile given the concurrent positive effects of OCA on other metabolic factors such as a decrease in hs-CRP (in PBC studies), and relative improvement of triglyceride and very low-density lipoprotein (VLDL) cholesterol levels. In order to better assess cardiovascular risk, longer treatment periods and larger numbers of subjects are necessary and are being studied further.**	

Section	Original Text (Version 10.0, 03 Feb 2020)	Revised Text (Version 11.0, 04 May 2021)	Key Change Reasons/ Justification for Change
		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 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. 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.**	

Section	Original Text (Version 10.0, 03 Feb 2020)	Revised Text (Version 11.0, 04 May 2021)	Key Change Reasons/ Justification for Change
Synopsis Section 6.4 Section 12 Section 15.1.7	6.4. Primary Objective Assessed at End of Study • To evaluate the effect of OCA compared to placebo on 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): - Death (all cause) - Model of end stage liver disease (MELD) score ≥15 - Liver transplant - 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) - ~~Histological~~ progression to cirrhosis	6.4. Primary Objective Assessed at End of Study • To evaluate the effect of OCA compared to placebo on 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): - Death (all cause) - Model of end stage liver disease (MELD) score ≥15 - Liver transplant - 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) - Progression to cirrhosis	The definition of progression to cirrhosis was made broader to not only include histology findings, but also laboratory parameters and clinical features as indicators of progression to cirrhosis. These broader criteria will now be used to identify events for adjudication by the Hepatic Outcomes Committee
[redacted]			

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	[redacted] ~~- Incidence of adjudicated cardiovascular events~~ ~~- Long-term safety and tolerability (TEAEs, ECGs, vital signs, and clinical laboratory assessments)~~ [redacted]	• **6.7. Safety Objectives Assessed at End of Study** • **To evaluate the effect of OCA compared to placebo on:** o **Incidence of adjudicated cardiovascular events** o **Incidence of adjudicated acute kidney injury events** o **Incidence of adjudicated events of hepatic injury** o **Long-term safety and tolerability (TEAEs, ECGs, vital signs, and clinical laboratory assessments)**	[redacted]
Synopsis Section 7.1 Section 7.1.3 Section 16.2	Final analysis will evaluate the effect of OCA on mortality and liver-related clinical outcomes and long-term safety of OCA after the accrual of approximately 291 adjudicated clinical outcomes	Final analysis will evaluate the effect of OCA on mortality and liver-related clinical outcomes and long-term safety of OCA after the accrual of approximately 291 adjudicated clinical outcomes	Study duration updated to 10 years based on current estimates for outcome accrual

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	composite events combined in the OCA 25 mg and placebo groups for subjects with fibrosis stage 2 or stage 3 (projected to take approximately ~~7~~ years in total). Subjects are expected to have a minimum follow-up time of approximately 4 years.	composite events combined in the OCA 25 mg and placebo groups for subjects with fibrosis stage 2 or stage 3 (projected to take approximately **10** years in total). Subjects are expected to have a minimum follow-up time of approximately 4 years.	
Section 7.1.2, Table 1	Schedule of Study Procedures For Clinical and Laboratory Evaluations – All Subjects • Urinalysis was updated from annual procedures to semi-annual procedures • Additional row was added for "**Educate Subjects on Signs and Symptoms of Intercurrent Illness (Appendix C)**" which occurs at all semi-annual visits • Additional row was added for "**Evaluate Signs and Symptoms of Intercurrent Illness**" which occurs at all semi-annual visits and EOS/EOT • [redacted] For Clinical Evaluations – For Subset of Subjects • [redacted] (Only at sites where device is available) additional assessment was added to the column "Semi-Annual/Annual" with footnote specifying "**These assessments are to be performed only annually (Months 30, 42, 54, 66, 78 and every 12 months until EOS).**" Footnotes [redacted]		Schedule of study procedures was updated to reflect changes to renal monitoring including the frequency of the urinalysis to occur semi-annually Education and assessment of intercurrent illness at each study visit (semi-annual) was added to reflect increased subject education and monitoring Fibroscan was updated to occur annually to support changes in hepatic injury monitoring

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	[ab] Additional CPK samples may be collected if ALT, total bilirubin, or ALP are elevated (see Table 2).		
Section 7.4	AEs, signs and symptoms of ~~suspected~~ hepatic injury or decompensation, and laboratory values will be reviewed at regular intervals as described in the following subsections (Section 7.4.1 to Section 7.4.2.1). Based on the assessments of signs and symptoms of hepatic injury (Appendix C) and liver biochemistry, investigational product will be continued, interrupted, or discontinued per criteria discussed in Section 7.7, and close monitoring procedures will be implemented (refer toSection 7.4.3). In the event hepatic injury ~~is suspected~~, the subject should be promptly brought into the	AEs, signs and symptoms of **potential** hepatic injury or decompensation, and laboratory values will be reviewed at regular intervals as described in the following subsections (Section 7.4.1 to Section 7.4.2.1). Based on the assessments of signs and symptoms of hepatic injury (Appendix C) and liver biochemistry, investigational product will be continued, interrupted, or discontinued per criteria discussed in Section 7.7, and close monitoring procedures will be implemented (refer to Section 7.4.3). In the event **of a potential** hepatic injury, the subject should be promptly brought into the clinic to	Instructions added to encourage subjects to seek immediate medical attention Symptoms update to reflect changes in DILI algorithm and for consistency with Appendix C

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	clinic to undergo a complete evaluation including laboratory assessments, physical examinations, and review of signs and symptoms of ~~suspected~~ hepatic injury or decompensation. 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 of the signs and symptoms during the study. 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. 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, 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, or severe fatigue, weakness, loss of appetite	undergo a complete evaluation including laboratory assessments, physical examinations, and review of signs and symptoms of **potential** hepatic injury or decompensation. 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 of the 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. 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,	

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	• 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: • Worsening or new pruritus • ~~Worsening of renal function or likely dehydration~~	weight loss, fever and chills, worsening, or new, or severe 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**	
Section 7.4.1	Liver biochemistry 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 in the event of signs or symptoms of ~~suspected~~ hepatic injury, decompensation, or if laboratory alerts have been triggered It is important that the laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. 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 lab is ~~permissible at the discretion of the Investigator~~. In these	**Events of potential as hepatic injury will be reviewed and adjudicated by the Hepatic Safety Adjudication Committee (HSAC), as described in Section 16.11. The specific criteria for identification and adjudication of potential hepatic injury events are described in the HSAC charter.** Liver biochemistries 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 in the event of signs or symptoms of **potential** hepatic injury, decompensation, or if laboratory alerts have been triggered It is important that the laboratory assessments be completed as required and that the central laboratory	Process for identifying potential hepatic injury and the action taken with IP was updated to align with published guidance

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	cases, the Investigator will obtain the laboratory results and the laboratory normal ranges. The process for assessing subjects using specific 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 2. … If any subject meets the triggering threshold limits ~~for either conjugated bilirubin or creatinine~~, investigational product should be immediately interrupted (see Section 7.6 for dosing modifications). ~~For the remaining liver biochemistry assessments, if a subject is outside of the upper or lower threshold limits, the laboratory assessment should be repeated in 2 to 3 days (with the exception of alkaline phosphatase [ALP], which is 7 days) and evaluated when the results are available.~~ 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 within the applicable threshold criteria~~, no dosing modifications are required and the subject should continue to be monitored. • If on repeat evaluation, ~~values~~ remain ~~outside the specified threshold~~ (see Table 2), investigational product ~~should~~ be interrupted for	be used for assessments whenever possible. 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. 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 subjects using specific 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 2. … If any subject meets the triggering threshold limits **indicated in Table 2 and experiences signs or symptoms of hepatic injury (severe fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, eosinophilia)** investigational product should be immediately interrupted (see Section 7.7 for dosing modifications).	

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	a minimum of 30 days ~~or until the laboratory results return to within the applicable threshold criteria (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) should be 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. The original or copies ~~can~~ be retained at the site as the source documents. 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	**If no signs or symptoms of hepatic injury 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 2**. 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 lab 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, the Medical Monitor should be promptly contacted upon awareness for consultation regarding management of the subject.** • If on repeat evaluation **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 2), investigational product **must** be interrupted for a minimum of 30	

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	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 ~~Suspected~~ DILI Management Algorithm may be adjusted, in which case specific guidelines will be provided to the sites for implementation.	days, [redacted] 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 in whom close monitoring is initiated, a follow-up assessment of the subject's**	

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		status should be performed after approximately 12 months of monitoring. 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.** The original or copies **should** be retained at the site as the source documents. **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.	

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		Specific aspects of the **Potential** DILI Management Algorithm may be adjusted, in which case specific guidelines will be provided to the sites for implementation.	
7.4.1, Figure 2	Figure 2: ~~Suspected~~ **Potential** DILI Management Algorithm for Study 747-303 *The following major changes were made to the figure:* • *"Conjugated bilirubin/creatinine" was replaced with "presence of signs and symptoms of hepatic injury", 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 7.4.1, Table 2	Table 2: 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 7.4.2 Section 9.9.5 Section 9.9.6 Section 13.1	Investigators will closely monitor subjects for potential progression to cirrhosis at every visit (or at unscheduled visits ~~in the event of signs or symptoms of suspected hepatic injury or decompensation~~). If the subject meets one or more of the criteria for progression to cirrhosis described in Figure 3 ~~based on review of laboratory values, noninvasive scores of liver fibrosis, transient elastography reading (if available)~~, and any additional evidence that may be available including findings from targeted physical exams or from clinically indicated procedures (eg, biopsy, ultrasound, or	Investigators will closely monitor subjects for potential progression to cirrhosis at every visit (or at unscheduled visits in the event of signs or symptoms of suspected hepatic injury or decompensation). If the subject meets one or more of the criteria for **potential** progression to cirrhosis described in Figure 3 and/or any additional evidence that may be available including findings from targeted physical exams or from clinically indicated procedures (eg, biopsy, ultrasound, or esophagogastroduodenoscopy [EGD]), then the subject is considered to have **potentially** progressed to cirrhosis; Child-Pugh scores must then be	Section updated to distinguish when a confirmatory liver biopsy is recommended. Stronger language was added to emphasize the need and importance of obtaining a liver biopsy to confirm cirrhosis and for inclusion in the

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	esophagogastroduodenoscopy [EGD]), then the subject is considered to have progressed to cirrhosis; Child-Pugh scores must then be assessed. Refer to Section 7.4.2.1 for determination of Child Pugh Score. Dose adjustments or investigational product discontinuation may be required in subjects who meet criteria for progression to cirrhosis (see Table 5). If ~~clinical~~ indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy be obtained and sent for central reading. The process for assessing disease progression to cirrhosis and the implications on dosing ~~is~~ summarized Figure 3.	assessed. Refer to Section 7.4.2.1 for determination of Child Pugh Score. **If a subject may have progressed to cirrhosis, a Fibroscan assessment should be performed where possible (if not already part of the scheduled assessment) and repeated annually.** Dose adjustments or investigational product discontinuation may be required in subjects who meet criteria for progression to cirrhosis (see Table 4). [redacted] If **non-invasive** indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy **should** be obtained and sent for central reading **to confirm the diagnosis of cirrhosis and for inclusion in the analysis of study outcomes. Any interpretations by a local pathologist should be collected and entered in the eCRF within 2 days of receiving results. If a biopsy is not performed, the reason should be stated in the eCRF. The following clinical outcomes may preclude the need for a liver biopsy to confirm progression to cirrhosis: presence of ascites, hepatic encephalopathy, variceal hemorrhage, or the presence of large esophageal varices or varices with a red wale that require treatment.**	analysis of study outcomes

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		The process for assessing disease progression to cirrhosis, **the potential need for liver biopsy,** and the implications on dosing is summarized Figure 3. **Potential events of progression to cirrhosis will be reviewed and adjudicated by the Hepatic Outcomes Committee which is described in Section 16.11. The Hepatic Outcomes Committee charter describes the specific criteria for identification and adjudication of potential events of progression to cirrhosis.**	
Section 7.4.2, Figure 3	Figure 3: Algorithm for Determining Progression to Cirrhosis *New figure to clarify when a confirmatory liver biopsy is recommended.* *Definition of "persistent" expanded to include 2 consecutive visits within 6 months.*		
Section 7.4.3	*Version 10 Section 7.7 Close Observation* At a minimum, the following assessments should be conducted at each study visit: • ~~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 …	*Version 11 Section 7.4.3 Close Observation* 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** (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 7.4.1).** … **For all subjects in whom close monitoring is initiated for potential hepatic injury, a follow-up**	The close observation section is specific to potential hepatic injury and was therefore reorganized 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

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		assessment of the subject's status should be performed after approximately 12 months of monitoring	
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 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).~~	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 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)**	Clarification added to capture when subjects are allowed to re-initiate IP

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		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 Section 15.1.11	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 local standard of care. The Investigator should contact the Medical Monitor upon awareness of treatment-emergent acute or nonacute pancreatitis.	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.	Revised to emphasize that data used to diagnose pancreatitis must be collected

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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, 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 4.**	Guidance provided on monitoring and actions for IP interruption and PK sample collection for renal impairment and nephrolithiasis

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		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**	

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		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 16.11). The specific criteria for identification and adjudication of potential AKI events are described in the Renal Adjudication Committee charter.** • [redacted] **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**	

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		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 (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.	

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		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 4	Figure 4: 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.		
Section 7.7	Subjects can be temporarily or permanently discontinued from investigational product by the Investigator at any time for clinical safety concerns.	Subjects can be temporarily or permanently discontinued from investigational product by the Investigator at any time for clinical safety concerns. [redacted]	Added PK sample collection to better understand exposure-response relationship.
Section 7.7, Table 4	Table 4: 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		
Section 8.2	Refer to Section 7.4 and Section 7.7 for withdrawal criteria related to ~~suspected~~ hepatic injury and/or decompensation; progression to cirrhosis; 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, and bariatric surgery, ~~and pregnancy~~. Other reasons,	Refer to Section 7.4 and Section 7.7 for withdrawal criteria related to **potential** hepatic injury and/or decompensation; progression to cirrhosis; treatment-emergent acute or nonacute pancreatitis; Grade 3 pruritus, AEs ≥Grade 3 in severity and possibly, probably, or definitely related to investigational product; liver transplantation, **and** bariatric surgery. Other reasons, including withdrawal of consent or lost to follow up, are described in Section 8.2.1 to Section 8.2.3 below.	Corrected to align with Section 7.7 as AEs >= Grade 4 and pregnancy are listed as interruptions not as withdrawal/discontinuation

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	including withdrawal of consent or lost to follow up, are described in Section 8.2.1 to Section 8.2.3 below.		
Section 9.3	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). 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.	**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 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 15.1.5.1.** **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.** **9.3.2. Other Concomitant Medications** 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	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 update ot reflect changes in progression to cirrhosis and guidance regarding COVID-19 vaccination was added.

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		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 **non-invasive** indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a **liver** biopsy **should** be obtained and sent for central reading (**refer to Section 7.4.2**). **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).**	
Synopsis Section 9.3.3	~~• 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.~~ *New Section and Figure*	**9.3.3. 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 participants as indicated via appropriate medicinal interventions (eg, statins). Recent guidelines stress the importance of evaluating atherosclerotic cardiovascular disease (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 low-density lipoproteins, are part of a comprehensive cardiovascular risk 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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		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 5).	
Section 9.3.4	*New Section*	**9.3.4. 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**	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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		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 the patient-centered care.**	

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		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 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 9.5.1	The DMC (refer to Section 16.10) ~~will have access to the IWRS and will be able to unblind individual subjects . The DMC~~ will be provided unblinded data to review during closed sessions. The DMC will document, in the closed session DMC minutes (which will be made available to the Sponsor only after the database is locked and the study is unblinded), details about any unblinded subject data reviews. Cases of	The DMC (refer to Section 16.10) will be provided unblinded data to review during closed sessions. The DMC will document, in the closed session DMC minutes (which will be made available to the Sponsor only after the database is locked and the study is unblinded), details about any unblinded subject data reviews. Cases of premature unblinding (as noted above) will be reviewed by the DMC.	Corrected per changes in Section 16.10.

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	premature unblinding (as noted above) will be reviewed by the DMC.		
Section 7.1.2, Table 1 Section 9.9.1, Table 5 Section 9.9.8.1 Section 9.9.8.3 Section 9.9.9	Semi-Annual Procedures (Months 24, 30, 36, 42, 48, 54, 60, 66, 72, ~~and~~ 78) Additional Annual Procedures (Months 30, 42, 54, 66, ~~and~~ 78) t	Semi-Annual Procedures (Months 24, 30, 36, 42, 48, 54, 60, 66, 72, 78 **and every 6 months until the EOS)** Additional Annual Procedures (Months 30, 42, 54, 66, 78 **and every 12 months until the EOS)**	Semi-annual and annual procedures updated to remove Month 78 as last timepoint. Study is ongoing until number of clinical outcome events is documented.
Section 7.1.2 Section 9.9.3 Section 9.9.4 Section 9.9.5 Section 9.9.6 Section 9.9.7 Section 9.9.8	• Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted)	• Instruct the subject to fast overnight (at least 8 hours) before the next visit (water is permitted **and subjects should ensure they are hydrated prior to study visits**)	Instructions for subjects to stay hydrated updated to encourage accurate monitoring for renal impairment and nephrolithiasis
Section 9.9.8.1	Semi-Annual Visit procedures for all subjects are as follows: • Verify that the subject has fasted for at least 8 hours … • Obtain blood samples for • [redacted] • Serum chemistry, hematology, and coagulation • Glucose and HbA1c • Educate subjects about signs and symptoms of hepatic injury or	Semi-Annual Visit procedures for all subjects are as follows: • **In the days leading up to and including the visit day, subjects should maintain the regular daily timing of their investigational product dose administration (eg, dosing every morning, dosing every afternoon, dosing every evening, etc). If the subject's regular daily dosing time occurs during the site visit, the subject should administer the dose at the study site and the time of dosing should be recorded in the eCRF.** • Verify that the subject has fasted for at least 8 hours …	[redacted] Section updated to reflect changes in education of intercurrent illnesses other than hepatic injury.

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	decompensation (as needed, per Investigator's discretion)
	• Evaluate signs and symptoms of ~~suspected~~ hepatic injury or decompensation and assess subjects per Suspected DILI Management and Progression to Cirrhosis Algorithm
	  • In subjects who progress to cirrhosis and have a CP score <7, 1 PK blood sample will be obtained at the next scheduled visit prior to dose adjustment. Subjects who discontinue investigational product due to progression to cirrhosis and Child Pugh score ≥7 or due to hepatic injury, will provide a PK blood sample ~~if the site visit is~~ within 7 days from dose interruption or discontinuation. The time of the last dose of investigational product prior to the PK blood sample will be reported.
	• Calculations will be performed by the Sponsor or designee for:
	• MELD score
	• [redacted]
	• Perform a urine-based β-hCG pregnancy test for females of childbearing potential
		• Obtain blood samples for
		  - [redacted]
		  - Serum chemistry, hematology, and coagulation
		  - Glucose and HbA1c
		  - [redacted]
		• Educate subjects about signs and symptoms of hepatic injury or decompensation (as needed, per Investigator's discretion) **and intercurrent illness and/or potential adverse events (Appendix C)**
		• [redacted]
			Frequency of urinalysis updated to reflect changes to renal monitoring

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		[redacted] • Calculations will be performed by the Sponsor or designee for: - MELD score - [redacted] • **Obtain urine sample for urinalysis** • Perform a urine-based β-hCG pregnancy test for females of childbearing potential	
Section 9.9.8.3	• Calculations will be performed by the Sponsor or designee for - Cardiovascular risk scores (FRS, Reynolds score, SCORE, 10-year ASCVD Risk) ~~• Obtain urine sample for urinalysis~~	• Calculations will be performed by the Sponsor or designee for - Cardiovascular risk scores (FRS, Reynolds score, SCORE, 10-year ASCVD Risk) **Annual procedures for the various subsets of subjects are as follows:** • [redacted]	Added annual Fibroscan assessment to better monitor subjects for progression to cirrhosis. Frequency of urinalysis updated to reflect changes to renal monitoring
Section 9.9.9	• Obtain blood samples for - [redacted] - Serum chemistry, hematology, and coagulation - Thyroid hormones - Free fatty acids	• Obtain blood samples for - [redacted] - Serum chemistry, hematology, and coagulation - Thyroid hormones - Free fatty acids	[redacted] Procedure for evaluation of intercurrent illness

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	[redacted]		
Section 9.9.10	The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted (refer to Section 7.4). Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. Evaluations may include a physical	The Investigator may schedule an at-clinic Unscheduled/Safety Visit at any time if clinically warranted (refer to Section 7.4). Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. Evaluations may include a physical exam, serum	

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	exam, serum biochemistry, serum electrolytes, ~~and~~ assessment of MELD scores at Investigator's discretion. Further monitoring outside of regular scheduled visits should be based on the Investigator's assessment of the subject's clinical status.	biochemistry, serum electrolytes, assessment of MELD scores, **and imaging and/or Fibroscan** at Investigator's discretion. **In these cases, where a local laboratory is used, it is important that all local laboratory data, including the reference ranges, are collected and entered in the eCRF within 2 days of receiving the results.** Further monitoring outside of regular scheduled visits should be based on the Investigator's assessment of the subject's clinical status.	
Section 10	*New Section.*	**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**	Guidance to Investigators on acceptable procedures and necessary documentation required during COVID-19 pandemic and vaccine information were added to ensure the safety of the subject in the study as well as the integrity of the study.

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		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 a qualified healthcare professional who is currently authorized to undertake examinations**	

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		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 within 2 days of receiving results. 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 of direct and total bilirubin, AST, ALT, GGT, ALP, coagulation panel (INR, aPTT), platelets, albumin and serum creatinine and non-liver safety labs of CBC & Diff, standard electrolytes, lipid panel 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**	

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		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, 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**	

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		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 the 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 the pediatric population suffering from biliary atresia (BA), there are no safety data available specific to use of COVID-19 vaccines in PBC, NASH subjects or in children suffering from BA.** **If a subject receives a COVID-19 vaccination, the date(s) of vaccination, vaccine name and manufacturer should be recorded as a concomitant medication for each dose.**	
Section 13.1	The investigator will assess the clinical criteria for progression of fibrosis to cirrhosis for each	The investigator will assess the clinical criteria for progression of fibrosis to cirrhosis for each subject	[redacted]

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	subject during the study. If clinical indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy be obtained and sent for central reading. Updated guidance on criteria to trigger an unscheduled liver biopsy in subjects with ~~suspected~~ progression to cirrhosis may be provided to investigators separately.	during the study. If clinical indicators of progression to cirrhosis become evident at any time during the study, it is recommended that a liver biopsy be obtained and sent for central reading. Updated guidance on criteria to trigger an unscheduled liver biopsy in subjects with **potential** progression to cirrhosis may be provided to investigators separately. [redacted]	[redacted]
Synopsis Section 13.1.1	In addition to the primary scoring system of NASH CRN, biopsy samples will also be scored based on modified Ishak scoring (Ishak 1995) and SAF scoring (Bedossa 2014) for all subjects as well as for quantitative collagen for a subset of subjects as exploratory assessments. Any extra biopsy tissue may undergo exploratory histological evaluations such as alpha-smooth muscle actin or bile acid transporter analysis	In addition to the primary scoring system of NASH CRN, biopsy samples **from the Month 18 Interim Analysis** will also be scored based on modified Ishak scoring (Ishak 1995) and SAF scoring (Bedossa 2014) for all subjects as well as for quantitative collagen for a subset of subjects as exploratory assessments. Any extra biopsy tissue may undergo exploratory histological evaluations such as alpha-smooth muscle actin or bile acid transporter analysis	Added language to clarify additional scoring on biopsy sample was for Month 18 Interim Analysis only
[redacted]			

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	[redacted]		

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		[redacted]	
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**.	Language expanded to include full list of symptoms subject and Investigator should be aware of per Appendix C.

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Section 15.1.1.3	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 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	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 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 [redacted]	Removal of immediately, as any life threatening event is considered serious [redacted]

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		[redacted]	
Section 15.1.5.1	Since pruritus is a subjective symptom, the occurrence and magnitude of which are not readily measured objectively, 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. Guidance for the management of subjects experiencing significant pruritus are provided in Table 4 (Section 7.4.2.1) and includes: • Pruritus ≥Grade 3 in severity: Discontinue investigational product • Pruritus ≤Grade 2 in severity: One or more of the following may be considered: - Drug holiday or less frequent dosing at the discretion of the Investigator. - ~~BAS prescription: Subjects taking BAS (including cholestyramine 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.~~	Since pruritus is a subjective symptom, the occurrence and magnitude of which are not readily measured objectively, 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. Guidance for the management of subjects experiencing significant pruritus are provided in Table 5 (Section 7.7) and includes: • Pruritus ≥Grade 3 in severity: Discontinue investigational product • Pruritus ≤Grade 2 in severity: One or more of the following may be considered: - Drug holiday or less frequent dosing at the discretion of the Investigator. - **Short-term use of BAS** o **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**	Since the long-term use of BAS can affect the exposure to OCA, guidance was added to 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 therapies may be ~~tried~~, as deemed clinically appropriate.	**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.** o **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.** o **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.** o **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 9.3.**	

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		- Other **medical** therapies 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 15.1.11	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 cholelithiasis 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 15.2.6	Blood, urine, and stool samples for laboratory assessments will be collected at the visits specified in Table 1. Full instructions concerning the number and type of samples to be collected at each visit, the required sample volumes, sample collection methods, sample	Blood, urine, and stool samples for laboratory assessments will be collected at the visits specified in Table 1. 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	Section updated to provide clarification on use of local lab and inclusion or results/reference ranges into the eCRF

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	processing, labeling, and shipping will be provided in separate procedural manuals. All necessary collection supplies will be provided by the appropriate 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 ~~manage subjects with clinically significant lipoprotein abnormalities using local standard of care procedures as appropriate after assessing the individual~~	will be provided in separate procedural manuals. All necessary collection supplies will be provided by the appropriate 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 indicate 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**	Monitoring of lipids language updated to reflect changes in Section 9.3.3

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	~~subject's total cardiovascular risk profile as described in Appendix A.~~	**reducing LDLc to reduce the risk and prevent onset or recurrence of ASCVD (refer to Section 9.3.3 and Appendix A).**	
Section 15.2.6, Table 12	*Table updated to include calculation of eGFR and PK analytes added for clarity based off updated renal monitoring and additional PK assessments.*		
Section 16.4.1	All efficacy analysis at EOS will be conducted using the ITT population (only including fibrosis stage 2 and 3 subjects). The hypothesis testing of primary and (key) secondary endpoints will be conducted in with control of Type 1 error (OCA 25 mg, then 10 mg). Adjustments for multiplicity are specified in Section 16.7 and additional details on the testing at EOS will be provided in the SAP. The primary efficacy endpoint at the EOS will be the time to first occurrence of one of the following post randomization: • Death (all-cause) • MELD score ≥15 • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) for onset of: - Variceal bleed - Hepatic encephalopathy (as defined by a West Haven score of ≥2) - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)	All efficacy analysis at EOS will be conducted using the ITT population (only including fibrosis stage 2 and 3 subjects). The hypothesis testing of primary and (key) secondary endpoints will be conducted in with control of Type 1 error (OCA 25 mg, then 10 mg). Adjustments for multiplicity are specified in Section 16.7 and additional details on the testing at EOS will be provided in the SAP. The primary efficacy endpoint at the EOS will be the time to first occurrence of one of the following post randomization: • Death (all-cause) • MELD score ≥15 • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) 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) • Progression to cirrhosis	The definition of progression to cirrhosis was made broader to not only include histology findings, but also laboratory parameters and clinical features as indicators of progression to cirrhosis. These broader criteria will now be used to identify events for adjudication by the Hepatic Outcomes Committee

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	• Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis) • ~~Histological~~ progression to cirrhosis		
[redacted]			
Section 16.9.2	*New Section*	**16.9.2. Hepatic and Renal Safety Adjudication** **Potential events of hepatic injury and AKI will be adjudicated during the study (Section 16.11). The adjudication of the events of hepatic injury will be separate from the adjudication of events for assessment of the primary outcomes endpoint 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 added to reflect additional adjudication committees.
Section 16.9.3	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 D and will be included in the Cardiovascular Adjudication Committee (CAC)	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	Definition of CV events for adjudication was updated to be consistent with the criteria defined in the CAC charter.

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	Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (See Section 16.11). Undetermined cause of death will be classified as a cardiovascular death by the CAC. … The time-to-event endpoints include:	adverse cardiovascular outcomes are defined in Appendix D and will be included in the Cardiovascular Adjudication Committee (CAC) Charter for adjudication. The adjudication of these events will be handled separately from the adjudication of events for assessment of the primary endpoint in this study (See Section 16.11). Undetermined cause of death will be classified as a cardiovascular death by the CAC. … The time-to-event endpoints include: • **Time from randomization to the first occurrence of arrhythmia**	
Section 16.10	The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data as well as the adjudication assessments from the ~~2~~ adjudication committees listed in Section 16.11. 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~~	The DMC will meet approximately quarterly at scheduled meetings and ad hoc meetings will be convened, as appropriate, to review safety and efficacy data as well as the adjudication assessments from the 4 adjudication committees listed in Section 16.11. 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	DMC responsibilities expanded to include review of aggregate analyses for all adjudication committees.

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	~~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 events resulting in death) are reviewed by the DMC in addition to a cumulative list of all SAEs.	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.**	
Synopsis, Section 16.11	All ~~suspected~~ liver-related clinical outcomes ~~and~~ MACE 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: • CAC: 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	All **potential** liver-related clinical outcomes, **and potential events of hepatic injury, AKI,** MACE, **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: • CAC: 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 **including clinical events and histological findings that are suspected as progression to liver cirrhosis**	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

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	to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee. Specific details of the events that will be adjudicated by the CAC, ~~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 outside of a protocol amendment. … 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. 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. Histological progression to cirrhosis will be determined by central reading of liver biopsies. A biopsy evaluation form signed by one of the study-specific central ~~pathology readers~~ will be	• **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. Specific details of the events that will be adjudicated by the CAC, 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 outside of a protocol amendment. … 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	adjudication committees.

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	necessary to confirm histological progression to cirrhosis. ~~This clinical outcome endpoint will not be~~ adjudicated by the Hepatic Outcomes Committee ~~but will be included in the adjudicated hepatic clinical outcomes events~~.	compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents. Histological progression to cirrhosis will be determined by central reading of liver biopsies. A biopsy evaluation form signed by one of the study-specific central **pathologists** will be necessary to confirm histological progression to cirrhosis. **Clinical events and histological findings of potential disease progression to cirrhosis will be** adjudicated by the Hepatic Outcomes Committee. **The end of study primary efficacy endpoints of clinical composite outcome events are described in Section 16.4.1.**	
Appendix A	This guidance summarizes recommendations for the management of LDL cholesterol based on the 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)~~.	This guidance summarizes recommendations for the management of LDL cholesterol based on the 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**	Appendix was reviewed and updated based on more recent US and European guidelines.

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		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.**	
Appendix B	*New Appendix.* *Inclusion of management of hyperglycemia appendix as a guidance to Investigators on the appropriate therapy be current guidelines.* Reference: **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	EDUCATION AND ASSESSMENT OF SIGNS/SYMPTOMS OF ~~HEPATIC INJURY AND/OR DECOMPENSATION~~ ~~Subject Education:~~ Subjects should be educated ~~on the signs and symptoms of hepatic injury and decompensation which are listed below. After Month 18, subjects determined to be at higher risk of progression or decompensation in the judgment of the Investigator may be monitored for signs and symptoms of suspected hepatic injury or~~	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.**	Appendix C updated to consolidate education and assessments for intercurrent illness that have been added to the protocol into one location for ease of use for the Investigator.

<table>
<tr><th>Section</th><th>Original Text (Version 10.0, 03 Feb 2020)</th><th>Revised Text (Version 11.0, 04 May 2021)</th><th>Key Change Reasons/ Justification for Change</th></tr>
<tr><td></td><td>~~decompensation more frequently than every 6 months (as frequently as needed) per discretion of the Investigator and upon discussion with the Medical Monitor.~~
~~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:~~
~~• Worsening or new pruritus~~
~~• Worsening of renal function or likely dehydration~~</td><td>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.
<table><tr><th>Events</th><th>Signs and Symptoms</th></tr><tr><td>Cholelithiasis
(Protocol Section 7.5.1)</td><td>• Upper abdominal pain or tenderness (particularly post-prandial), abdominal swelling, nausea, vomiting, or fever</td></tr><tr><td>Acute cholecystitis, or Acute pancreatitis
(Protocol Section 7.5.2)</td><td>• Symptoms of these events may be similar to symptomatic cholelithiasis (see Section 7.5.1)
• Significant upper abdominal pain with nausea, vomiting, or fever, jaundice</td></tr><tr><td>Hyperglycemia</td><td>• Polyuria, polydipsia, polyphagia, blurred</td></tr></table></td><td></td></tr>
</table>

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	~~Intercurrent Illness:~~ ~~In particular, intercurrent illnesses such as gastroenteritis may exacerbate hepatic injury or decompensation (eg, established severe abdominal pain, vomiting, and/or diarrhea for more than 4 days) and should be an indication for prompt drug interruption and complete subject evaluation.~~ ~~Subject Assessment:~~ ~~At each visit, study site staff should inquire if the subject has developed any of the above 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.~~ ~~Positive responses to any new or worsening symptoms among those listed above should solicit follow up questions. Follow up questions may include further questions on duration of experiencing the symptom, associated signs and symptoms, whether this is new or worsening from previous experience or other questions as appropriate. Some examples are provided below.~~ Follow up Questions for Positive Response to Signs/Symptoms of Hepatic Injury or Decompensation … 5. Example 5: If subject has noticed feeling dehydrated or is not urinating as often as usual, follow up question may include:	**(Protocol Section 9.3.4)**	**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])** • **More general signs and symptoms of ascites and**	

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	a. Are you excessively thirsty?	**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**	

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		Other Symptoms: • **Worsening or new pruritus** • **Decreased urine output, dizziness, or lethargy** ... 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?**	
SOC	*Removal of all previous SOCs* *Moving forward only the most recent SOC will be included in the protocol.*		