CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of NST-4016 in Patients With Nonalcoholic Steatohepatitis (NASH)

Investigational Product: NST-4016 Icosabutate

Protocol Number: NST-02

Sponsor:
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SIGNATURE PAGE

STUDY TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of NST-4016 in Patients With Nonalcoholic Steatohepatitis (NASH)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
Electronically signed by: STEPHEN ROSSI *Reason: Approved* *Date: Jul 21, 2022 14:40 PDT*	21-Jul-2022

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INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by NorthSea Therapeutics B.V. (hereinafter NorthSea) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to NorthSea and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by NorthSea, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration regulations, Institutional Review Board regulations, and International Council for Harmonisation Guidelines for Good Clinical Practice.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of NST-4016 in Patients With Nonalcoholic Steatohepatitis (NASH)

PROTOCOL NUMBER: NST-02

INVESTIGATIONAL PRODUCT: NST-4016 Icosabutate

PHASE: 2b

INDICATION: Nonalcoholic steatohepatitis (NASH) without cirrhosis

OBJECTIVES:

The primary objective is to evaluate the efficacy of different doses of NST-4016 on the resolution of NASH without worsening of fibrosis.

The secondary objective is to determine the safety and tolerability of NST-4016 in patients with NASH without cirrhosis.

POPULATION:

Inclusion Criteria

A patient who meets all of the following criteria will be eligible to participate in the study:

1. Provides signed written informed consent and agrees to comply with the study protocol.
2. Is a male or female aged 18 to 75 years, inclusive.
3. Has a histological diagnosis of NASH without cirrhosis prior to study entry, as confirmed by either of the following:
   a. A historical liver biopsy within 6 months of screening (and has not received any NASH treatment since the biopsy). The histology slides from the historical biopsy must be evaluable and available for review by the central pathology reader. Historical liver biopsies obtained during the course of a prior investigational drug study must not be utilized if obtained within 3 months or 5 half-lives of the last dose of the prior investigational drug, whichever is longer.

      OR

   b. A contemporaneous liver biopsy during the screening period (Week -8 to Week -1). Patients without a historical biopsy must also have a FibroScan® vibration-controlled transient elastography (VCTE) measurement ≥8.5 kPa and a controlled attenuation parameter (CAP) for steatosis with cut-off values ≥300 dB/m at screening or a historical FibroScan (with eligible VCTE and CAP values) within 90 days of screening (prior to moving forward with the magnetic resonance imaging [MRI]-proton density-fat fraction [PDFF] and subsequent liver biopsy).

Note: Prior to performing a contemporaneous liver biopsy, patients must have 3 or more of the following metabolic risk factors:

- Type 2 diabetes.
- Elevated fasting glucose (≥100 mg/dL).
- Elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg or on antihypertensive drug treatment).
- Fasting high-density lipoprotein-cholesterol (<40 mg/dL in men or <50 mg/dL in women or on drug treatment).
- Elevated fasting triglycerides (≥150 mg/dL but <300 mg/dL or on drug treatment).
- Elevated waist circumference (>40 inches in men and >35 inches in women) present before performing the biopsy.

4. Has a Nonalcoholic Fatty Liver Disease Activity Score (NAS) ≥4, with a score of at least 1 in each component (steatosis, lobular inflammation, and ballooning), as per the central pathology reader.
5. Has a fibrosis score F1 to F3, inclusive (F1 capped at 20%), on liver biopsy as per the central pathology reader.
6. Has a PDFF ≥8% on MRI at screening, per the central imaging reader. The MRI-PDFF criteria will not apply if the patient has a qualifying historical liver biopsy.
7. Has alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <5 × upper limit of normal (ULN) and AST ≥20 U/L in men and ≥17 U/L for women upon entry into the study. A documented AST ≥30 U/L by a local laboratory within 60 days of screening will also be acceptable. The minimum AST criteria will not apply if the patient has a qualifying historical liver biopsy.
8. Has stable baseline liver enzymes, including serum ALT, AST, alkaline phosphatase (ALP), and total bilirubin values that are established by at least 2 samples demonstrating the following:

   a. Values of an enzyme in the 2 samples are within 1.5 × ULN ranges.

      OR

   b. If one of the enzyme levels is >1.5 × ULN, the variability between the 2 samples of ALT and AST does not exceed 50% and the variability between the 2 samples of ALP and total bilirubin does not exceed 30%.

   Notes:

   - The 2 samples need to be obtained 2 to 16 weeks apart.
   - One sample can be obtained from the patient's medical history and 1 sample can be obtained during the screening period, or both samples can be obtained during the screening period.

- A third sample may be collected if the variability between the first 2 samples exceeds the limits in Inclusion Criterion 8b and one of these values is deemed spurious.

9. Has no other cause of chronic liver disease (eg, autoimmune disorder, alcoholic liver disease, drug-induced liver disease, primary biliary cholangitis, primary sclerosing cholangitis, hepatitis B virus, hepatitis C virus [HCV], Wilson's disease, α-1-antitrypsin deficiency, hemochromatosis) and has not had a liver transplant.
10. If the patient has type 2 diabetes mellitus (T2DM), he/she has stable T2DM, defined as hemoglobin A1c ≤9.5% at screening and no new symptoms associated with decompensated diabetes in the previous 3 months.
11. Has a stable body weight, defined by no more than a 5% loss in initial body weight for at least 3 months or since the liver biopsy was performed, whichever is longer.
12. Has a body mass index ≥25 kg/m^2 and ≤50 kg/m^2.
13. Is willing to undergo a liver biopsy after 52 weeks of treatment.
14. Is not of childbearing potential or, if of childbearing potential, is not pregnant as confirmed by a negative serum human chorionic gonadotropin test at screening and is not planning a pregnancy during the course of the study.

    Note: A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile (permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). A postmenopausal state is defined as no menses for ≥12 consecutive months without an alternative medical cause. A follicle-stimulating hormone level in the postmenopausal range will be used to confirm a postmenopausal state in women ≤55 years of age.
15. Male and female patients of childbearing potential must agree to use a dual method of contraception (a highly effective method of contraception in conjunction with a barrier contraception) consistently and correctly from the first dose of study drug until 90 days after the last dose of study drug. Highly effective methods of contraception are those that result in a failure rate of less than 1% per year when used consistently and correctly and include the following: hormonal intrauterine devices; hormonal contraceptives (oral birth control pills, depo, patch, or injectable); male sterilization performed more than 6 months prior to screening; and complete abstinence from sexual intercourse (if this is the patient's usual and preferred lifestyle). Barrier methods of contraception include male or female condoms used in combination with a separate spermicide product (eg, foam, gel, film, cream, or suppository).
16. Male patients must agree to abstain from sperm donation from the first dose of study drug until 90 days after the last dose of study drug.

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in the study:

1. Has a known history of alcohol abuse or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [1 unit of alcohol is equivalent to a half pint of beer {285 mL}, 1 measure of spirits {25 mL}, or 1 glass of wine {125 mL}]). Alcohol abuse will be defined as having an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score of ≥3 points for men and women AND a full Alcohol Use Disorders Identification Test (AUDIT) score of ≥8 points at screening.

   Note: Only patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.

2. Has had bariatric surgery within the past 5 years or has bariatric surgery planned to occur during the study.
3. Has significant systemic or major illnesses other than liver disease, including pulmonary disease, renal failure, organ transplantation, serious psychiatric disease, or malignancy that, in the opinion of the Investigator, would preclude treatment with NST-4016 or confound the study results. This would include any malignancy under evaluation, or diagnosed and/or treated within the past 2 years except for squamous or non-invasive basal skin cell or cervical carcinoma in-situ.
4. Has a recent (within 6 months) history of cardiac dysrhythmias and/or cardiovascular disease, including congestive heart failure (class C and D of the American Heart Association), unstable coronary artery disease, cerebrovascular disease, or myocardial infarction.
5. Has uncontrolled arterial hypertension.
6. Has hepatitis B surface antigen >0, HCV antibody and HCV polymerase chain reaction (PCR) >0 (HCV PCR only required for patients who test positive for HCV antibody; patients with a confirmed history of HCV infection can be included if HCV PCR has been negative for at least the last 2 years), or human immunodeficiency virus infection.
7. Has type 1 diabetes mellitus.
8. Has diabetic ketoacidosis.
9. Has a history of liver decompensation, such as ascites, esophageal varices, and hepatic encephalopathy.
10. Has any of the following exclusionary laboratory results upon entry into the study:
    a. Hemoglobin ≤11 g/dL for females and ≤12 g/dL for males.
    b. White blood cell count ≤2.5 K/μL.
    c. Neutrophil count ≤1.5 K/μL.
    d. Platelet count ≤150 K/μL.
    e. Total bilirubin ≥1.3 mg/dL. Patients with total bilirubin ≥1.3 mg/dL can be included if direct bilirubin is within normal ranges in the setting of Gilbert's syndrome.

f. Albumin <3.6 g/L.

g. International Normalized Ratio ≥1.3, unless due to anti-coagulant therapy.

h. Thyroid-stimulating hormone >1.5 × ULN.

i. Estimated glomerular filtration rate <60 mL/min/1.73 m^2.

j. Fasting triglyceride level >300 mg/dL.

Note: Repeat testing may be performed in consultation with the Medical Monitor if any of the above laboratory parameters are outside the specified ranges.

11. Has a hemostasis disorder.
12. Has any contraindication to liver biopsy or MRI.
13. Has any clinically significant electrocardiogram (ECG) abnormality at screening.
14. Has participated in any other investigational drug study within the previous 3 months or 5 half-lives of the last dose of the investigational drug, whichever is longer.
15. Has a known hypersensitivity to any of the ingredients or excipients of the study drug.
16. Has used any drug known to produce hepatic steatosis, including systemic corticosteroids, methotrexate, tetracycline, amiodarone, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid, for more than 2 weeks in the 6 months prior to screening. Local corticosteroid injection for musculoskeletal disorders is permitted, including epidural corticosteroid administration.
17. Is unable to comply with the following concomitant medication restrictions:
    a. Lipid-lowering therapies must be stable for ≥3 months at screening. Fish oil and other omega-3 compounds must also be stable for ≥3 months at screening if the dose is ≥1000 mg per day.
    b. Antidiabetic drugs, including insulin regimens, must be stable for ≥3 months at screening, with the exception of sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 agonists, which must be stable for ≥6 months at screening.
    c. No vitamin E >400 U/d, pioglitazone, obeticholic acid, or antiobesity drugs for 3 months prior to screening or since the liver biopsy, whichever is longer.
18. Has any other condition that, in the opinion of the Investigator, would impede competence or compliance or possibly hinder completion of the study.
19. Uses any prohibited medications or any concomitant medications used to treat an exclusionary medical condition.

STUDY DESIGN AND DURATION:

This is a 62-week (including screening and follow-up), multicenter, randomized, double-blind, placebo-controlled, parallel-group study in male and female patients with a histological diagnosis of NASH.

The study includes a screening period, double-blind treatment period, and post-treatment follow-up. The Screening Visit will occur up to 8 weeks prior to randomization at Visit 2

(Week 0); more than 1 Screening Visit may be necessary to perform all required procedures. The double-blind treatment period will entail 52 weeks of dosing with study drug and will be followed by a Safety Follow-up Visit 2 weeks after the last dose of study drug.

Approximately 264 patients who meet the eligibility criteria will be randomized into 1 of 3 parallel treatment groups, each of which will contain approximately 88 patients. Patients in Group 1 will receive 300 mg NST-4016, patients in Group 2 will receive 600 mg NST-4016, and patients in Group 3 will receive placebo. Patients will be stratified by biopsy fibrosis score (2 levels: F1 versus F2 or F3).

Baseline assessments will include hepatic imaging (MRI-PDFF and iron-corrected T1 [cT1]), liver biopsy, vital signs (blood pressure, pulse rate, and body temperature), physical examinations, laboratory evaluations (hematology, biochemistry, coagulation, and lipid panels and urinalysis), and 12-lead ECGs. Historical liver biopsy within 6 months of screening may be used for eligibility if evaluable histology slides are available for review by the central pathology reader. Historical liver biopsies obtained during the course of a prior investigational drug study must not be utilized if obtained within 3 months or 5 half-lives of the last dose of the prior investigational drug, whichever is longer. Patients who screen fail may be rescreened once. With the exception of MRI-PDFF, cT1, and liver biopsy, baseline assessments will be collected at Visit 2 (Week 0, Day 0), prior to dosing; for MRI-PDFF, cT1, and liver biopsy, the assessments performed during screening will provide the baseline data.

Study drug dosing will begin at Visit 2 (Week 0, Day 0) and will continue daily for 52 weeks. During the 52-week treatment period, patients will return to the clinic for study visits every 1 to 3 months. The following assessments will occur at every study visit during the treatment period: adverse events, concomitant medications, body weight, vital signs, physical examinations, laboratory evaluations (hematology, biochemistry, coagulation, and lipid panels and urinalysis), and trough pharmacokinetic (PK) sampling. For a subset of patients (approximately 8 patients per group) at pre-identified sites, blood samples for analysis of additional PK parameters will also be collected predose and up to 24 hours postdose at Visit 2. In addition, hepatic imaging will be performed at Visit 5 (after 16 weeks of treatment) and Visit 9 (after 52 weeks of treatment).

Evaluation of liver inflammation and fibrosis biomarkers (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR], high-sensitivity C-reactive protein [hsCRP], N-terminal type 3 collagen propeptide [Pro-C3], and enhanced liver fibrosis [ELF] panel) will be performed at Visits 2, 5, and 9. Twelve-lead ECGs will be performed at Visits 2, 5, 7, and 9, and a liver biopsy will also be performed at Visit 9. Throughout the study, patients will be monitored for suspected drug-induced liver injury.

A Safety Follow-up Visit (Visit 10) will occur 14 days after the last dose of study drug to assess adverse events, concomitant medications, body weight, vital signs, physical examination findings, laboratory parameters, and 12-lead ECGs. Lipid parameters will be monitored throughout the follow-up period and will be managed by the Investigator.

Patients who discontinue early from the study for any reason prior to completion of the treatment period will be requested to return to the clinic for an Early Termination (ET) Visit as soon as possible after their last intake of study drug. Patients who discontinue early from the study for any reason after completion of the treatment period and before the Safety Follow-up Visit will be

requested to return to the clinic for an ET Visit as soon as possible and no later than the planned Safety Follow-up Visit.

From screening through follow-up, the total study duration for each patient who completes the entire treatment period will be approximately 62 weeks.

An external, independent Data Safety Monitoring Committee (DSMC) will review all available unblinded preliminary safety and biomarker results per the DSMC Charter.

In addition, the following data was comprehensively reviewed during an interim analysis, which was performed after 90 patients had completed 16 weeks of treatment: ALT, AST, HOMA-IR, Pro-C3, ELF panel, MRI-PDFF, cT1, and lipid parameters.

This study protocol includes contingency measures to manage disruptions due to Coronavirus Disease 2019 (COVID-19) control measures; see Appendix G for details. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

All patients will take 2 capsules of study drug (either 300 mg NST-4016 and/or matching placebo) orally in the morning with water once daily for 52 weeks.

EFFICACY VARIABLES:

The primary efficacy parameter is the percentage of patients with resolution of NASH, defined as disappearance of ballooning (score = 0) with lobular inflammation score 0 or 1, with no worsening of fibrosis.

The secondary efficacy parameters include the following:

- Change from baseline in NAS
- Changes in individual histological scores for steatosis, ballooning, inflammation, and fibrosis
- Changes in the liver enzymes AST, ALT, gamma glutamyl transferase, and bilirubin
- Changes in the imaging parameters MRI-PDFF and cT1
- Changes in the inflammation marker hsCRP
- Changes in the fibrosis activity markers Pro-C3 and ELF panel
- Changes in HOMA-IR, a measure of insulin resistance and metabolic status

Exploratory Biomarker Analysis

The exploratory parameters include the following (in a subgroup of patients):

- Profile and characterization of lipid species on End of Treatment Visit liver biopsy
- Profile and characterization of lipid species on baseline and End of Treatment serum samples

PHARMACOKINETIC VARIABLES:

For all patients, blood samples for evaluation of trough plasma PK concentrations of NST-4016 will be collected predose at Visits 2 to 9 (or the ET Visit, if applicable).

For those patients participating in the intensive PK subset, PK blood samples will be collected in relation to the first dose of study drug at Visit 2. Samples will be taken at the following timepoints: predose (within 1 hour prior to the first dose), followed by 1, 2, 3, 4, 6, and 8 hours postdose (±10 minutes) at Visit 2 (Day 0) and 24 hours postdose (±1 hour, but prior to the second dose of study drug on Day 1).

For the intensive PK subset of patients, the following PK parameters will be calculated in order to further characterize the PK of NST-4016 after the first dose:

- $AUC_{0\text{-}t}$: area under the plasma concentration-time curve from time 0 to the time of the last observed concentration
- $AUC_{0\text{-}inf}$: area under the plasma concentration-time curve from time 0 extrapolated to infinity
- CL/F: apparent plasma clearance
- C_{max}: maximum observed plasma concentration
- T_{max}: time to reach the maximum observed plasma concentration
- V_z/F: apparent volume of distribution

Additional PK parameters may be determined, if deemed appropriate.

SAFETY VARIABLES:

Safety assessments will include the monitoring of adverse events, serious adverse events (SAEs), vital signs (blood pressure, pulse rate, and body temperature), physical examinations, 12-lead ECGs, and clinical laboratory parameters (hematology, biochemistry, coagulation, and lipid panels and urinalysis).

Throughout the study, all treatment-emergent adverse events (TEAEs), clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for suspected drug-induced liver injury.

STATISTICAL ANALYSES:

Full details of the analyses will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock and unblinding.

Analysis Populations

The Randomized Population will include all patients who are randomized to the study.

The Intent-to-Treat (ITT) Population will include all patients who are randomized and receive at least 1 dose of study drug.

The Modified ITT (mITT) Population will include all patients from the ITT Population who have valid baseline and Week 52 (or ET, if applicable) liver biopsy measurements.

The Per-Protocol (PP) Population will include all patients from the mITT Population who complete the 52-week treatment period without any major protocol violations.

The Trough PK Population will include all patients who received at least 1 dose of NST-4016 and have at least 1 measurable trough PK concentration.

The Intensive PK Population will include all patients who received at least 1 dose of NST-4016 and have at least 1 measurable non-trough intensive PK sample.

The Safety Population will include all patients who receive at least 1 dose of study drug.

Efficacy Analysis

The efficacy analysis will be performed on the ITT Population; missing values for continuous endpoints will be imputed using multiple imputation methods.

Baseline will be defined as the value at the Screening Visit for measurements from the liver biopsy and imaging data and as the predose value at Visit 2 (Week 0) for the biomarker data. For other efficacy endpoints, baseline will be defined as the predose value at Visit 2 (Week 0); if this value is missing, then the latest predose value will be used.

Primary Efficacy Analysis

The primary endpoint (ie, the percentage of patients with resolution of NASH without worsening fibrosis) will be analyzed using the ITT Population. Patients without a Week 52 (or ET, if applicable) liver biopsy will be imputed as nonresponders. The number and percentage of patients meeting the criteria for the primary endpoint will be summarized by treatment group.

The primary analysis will be conducted using the data from the 600 mg NST-4016 and placebo groups using the Cochran-Mantel-Haenszel test, stratified by biopsy fibrosis score (2 levels: F1 versus F2 or F3). The primary analysis will be based on the use of a 2-sided test at the alpha=0.05 level of significance.

If the primary analysis is statistically significant ($p<0.05$), the key secondary analysis of the primary endpoint will be conducted using the data from the 300 mg NST-4016 and placebo groups, again using the Cochran-Mantel-Haenszel test, stratified by biopsy fibrosis score (2 levels: F1 versus F2 or F3). Due to the use of this fixed-sequence testing procedure, the key secondary analysis will be based on the use of a 2-sided test at the alpha=0.05 level of significance. However, if the primary analysis is not statistically significant, the comparison between the 300 mg NST-4016 and placebo groups will be exploratory rather than confirmatory.

A sensitivity analysis for the primary endpoint will be carried out using a logistic regression model with treatment group (300 mg NST-4016, 600 mg NST-4016, or placebo) and biopsy fibrosis score (2 levels: F1 versus F2 or F3) as factors. Pairwise treatment comparisons will be estimated in this model as odds ratios (NST-4016 versus placebo) along with their 95% confidence intervals and p-values.

The primary, key secondary, and sensitivity analyses of the primary endpoint will be repeated on the mITT and PP Populations.

Secondary Efficacy Analysis

Continuous efficacy variables will be summarized using descriptive statistics for the observed data and change and/or percent change from baseline by treatment group and visit as appropriate.

Change from baseline to Week 52 in NAS and individual histological scores will be analyzed in an analysis of covariance model, adjusting for treatment (300 mg NST-4016, 600 mg NST-4016, or placebo), biopsy fibrosis score (2 levels: F1 versus F2 or F3), and respective baseline score. Pairwise treatment comparisons between each NST-4016 dose and placebo will be estimated in this model using least square (LS) means, standard errors, 95% confidence intervals, and p-values. A similar analysis will be carried out for the imaging parameters at Week 16 and Week 52.

Efficacy variables measured at multiple timepoints will be analyzed with Mixed Model Repeated Measures methods, with change (or percent change) from baseline as the dependent variable, adjusting for treatment (300 mg NST-4016, 600 mg NST-4016, or placebo), biopsy fibrosis score (2 levels: F1 versus F2 or F3), and baseline score. Pairwise treatment comparisons between each NST-4016 dose and placebo at Week 52 will be estimated using LS means, standard errors, 95% confidence intervals, and p-values.

Exploratory Biomarker Analysis

The analysis of exploratory endpoints will be further described in the Statistical Analysis Plan.

Pharmacokinetic Analysis

Trough plasma PK concentrations at Visits 3 to 9 will be summarized descriptively by visit for the Trough PK Population.

For the subset of patients with intensive PK sampling data, additional PK parameters will be summarized by treatment using descriptive statistics for the Intensive PK Population. No formal statistical analysis of PK parameters will be performed.

Safety Analysis

Safety variables will be tabulated and presented for the Safety Population.

Baseline will be defined as the predose value at Visit 2 (Week 0); if this value is missing, then the latest predose value will be used.

A TEAE is defined as a new or worsening adverse event after the first dose of study drug. The number and percentage of patients with at least 1 TEAE will be summarized by treatment group by system organ class and preferred term. Similar summaries will be presented for study drug-related TEAEs and SAEs.

Safety laboratory parameters, vital signs, and ECGs will be summarized by treatment group by visit. Change from baseline values by visit will also be presented for the continuous parameters. The number (and percentage) of patients with abnormalities based on predefined normal ranges will be tabulated by treatment group.

Interim Analysis

An interim analysis was planned for this study after 90 patients had completed 16 weeks of treatment. This analysis was reviewed by the DSMC according to the DSMC Charter. The interim analysis included a comprehensive review of the following data: ALT, AST, HOMA-IR, Pro-C3, ELF panel, MRI-PDFF, cT1, and lipid parameters. The conclusions and recommendations of the DSMC were shared blindly with the Sponsor and clinical sites. A separate interim analysis plan was finalized prior to conducting the interim analysis.

Data Safety Monitoring Committee

An external, independent DSMC will review all available unblinded preliminary safety and biomarker results, as described in the DSMC Charter. The DSMC Charter will describe the overall guidelines, composition and roles, and responsibilities of the independent DSMC for the NST-02 study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study. Patient accrual will continue throughout the period of the DSMC review. The DSMC will advise on the accrual of the remaining patients per protocol or any amendments that are necessary for safety reasons.

SAMPLE SIZE DETERMINATION:

A sample size of 88 patients per treatment group provides 80% power to detect a 40% responder rate for active versus placebo, assuming a placebo response rate of 18% and a dropout rate of 25%.

SITES: Approximately 50 sites in the United States

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AA	Arachidonic acid
ACC	American College of Cardiology
AESI	Adverse events of special interest
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
BMI	Body mass index
CAP	Controlled attenuation parameter
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CSR	Clinical Study Report
cT1	Iron-corrected T1
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAG	Diglyceride
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
ELF	Enhanced liver fibrosis
EPA	Eicosapentaenoic acid
ET	Early Termination
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus

Abbreviation	Definition
HETE	Hydroxyeicosatetraenoic acid
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
hsCRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein-cholesterol
LS	Least square
mITT	Modified Intent-to-Treat
MRI	Magnetic resonance imaging
n-3 FA	Omega-3 fatty acid
NAS	Nonalcoholic Fatty Liver Disease Activity Score
NASH	Nonalcoholic steatohepatitis
PCR	Polymerase chain reaction
PCSK9	Proprotein convertase subtilisin kexin 9
PD	Pharmacodynamic
PDFF	Proton density-fat fraction
PK	Pharmacokinetic(s)
PP	Per-Protocol
PPARα	Peroxisome proliferator-activated receptor alpha
Pro-C3	N-terminal type 3 collagen propeptide
SAE	Serious adverse event
SEDDS	Self-Emulsifying Drug Delivery System
SGLT2	Sodium-glucose cotransporter-2
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor alpha
ULN	Upper limit of normal
VCTE	Vibration-controlled transient elastography
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

NorthSea Therapeutics B.V. (hereinafter NorthSea) is developing the drug substance icosabutate (International Nonproprietary Name) (development code NST-4016). Icosabutate is a novel, orally administered, semisynthetic fatty acid for the treatment of lipid disorders (hypertriglyceridemia, mixed dyslipidemia, and hypercholesterolemia) and nonalcoholic steatohepatitis (NASH).

1.1 Rationale

Icosabutate is a novel, orally administered, highly potent, semisynthetic fatty acid for the treatment of various dyslipidemias and NASH. Structural modification of the natural omega-3 fatty acid (n-3 FA) eicosapentaenoic acid (EPA) is designed to potentiate the pharmacological effects of naturally occurring n-3 FA by increasing direct hepatic delivery through the portal vein following absorption, reducing the incorporation into complex lipids, and increasing availability for fatty acid intracellular signaling pathways regulating metabolism, inflammation, and fibrosis.

The clinical experience with icosabutate shows potent hypolipidemic effects along with improvements in glycemic control. Additionally, marked decreases in elevated liver enzymes suggest that icosabutate has additional hepatoprotective effects not typically seen with hypolipidemic drugs. Similarly, the significant improvements in glycemic control observed in patients with severe hypertriglyceridemia in response to treatment with icosabutate is not observed with either unmodified EPA or cholesterol-lowering drugs. Beneficial effects on both plasma lipids and glycemic control with icosabutate are important attributes for the treatment of patients with NASH given the strong association of NASH with both cardiovascular disease and diabetes.

The nonclinical experience with icosabutate thus far indicates potent reductions in hepatic steatosis, inflammation, and fibrosis in multiple differentiated NASH models. There are likely multiple contributors to the observed pharmacodynamic (PD) effects of icosabutate in NASH. Although icosabutate is a partial peroxisome proliferator-activated receptor alpha (PPARα) agonist, the activation of which may underlie its beneficial effects on plasma triglycerides, the beneficial effects in fibrosing NASH are likely mediated via other mechanisms. However, PPARα activation does likely contribute to the increase in hepatic fatty acid β-oxidation and increase in ketone formation, which in turn may reduce the hepatic lipid load. Reductions in hepatic diglycerides (DAGs) and cholesteryl ester may also be partially related to PPARα, although icosabutate has potent effects upon hepatic cholesterol not seen with synthetic PPARα agonists.

Icosabutate induces highly significant improvements in hepatic inflammation, including reductions in proinflammatory gene expression along with decreases in hepatic inflammatory cellular infiltrates and galectin-3 content in rodent NASH models. The mechanisms underlying these effects may involve significant reductions in the hepatic levels of proinflammatory bioactive arachidonic acid (AA)-derived metabolites (ie, hydroxyeicosatetraenoic acids [HETEs]), which are associated with NASH in humans and rodents. The ability of icosabutate to remain as a free acid and avoid incorporation into complex lipids is believed to underlie its ability to potently target the AA cascade versus unmodified EPA.

Icosabutate also decreases the hepatic expression of pivotal genes regulating HETE and leukotriene formation (eg, 5-lipoxygenase activation protein and cytosolic phospholipase A2). In addition to the effects on hepatic inflammation, the reductions in proinflammatory AA metabolites may also underlie the improvements in insulin resistance and reductions in NASH-associated hepatic lipids such as DAGs. The formation of anti-inflammatory omega-3 cytochrome P450

(CYP) epoxides is also seen with icosabutate, which in concert with the reductions in AA metabolites, leads to a reversal of the balance between hepatic proinflammatory and anti-inflammatory fatty acid metabolites derived from the AA cascade.

Icosabutate significantly reduces, and even reverses, fibrosis in rodent models of NASH in association with a marked reduction in collagen fiber number. Significant reductions in the expression of pivotal profibrotic genes, such as COL1A1 and PDGFR1, are also observed in concert with the reduction in hepatic fibrosis. The reduction in hepatic fibrosis is likely secondary to the significant reduction in the number of proliferating stellate cells (ie, myofibroblasts) in the livers of rodents with established NASH after treatment with icosabutate. These effects are likely to be at least partially related to the above-mentioned anti-inflammatory effects. However direct antiproliferative effects are seen in isolated human stellate cells, which suggests that icosabutate has direct antifibrotic effects independent of effects on inflammatory cell types such as macrophages and/or dying hepatocytes.

The mechanism underlying the direct antifibrotic effects of icosabutate is not clarified. However, icosabutate functions as a potent hepatic antioxidant, inducing significant decreases in the amount of hepatic oxidized glutathione in multiple rodent NASH models. This occurs in concert with a highly significant increase in the reduced to oxidized glutathione ratio and increases in the hepatic expression of enzymatic antioxidant genes, such as SOD1, SOD2, and catalase. As oxidative stress sensitizes stellate cells to multiple proliferation-inducing stimuli such as tumor necrosis factor alpha (TNF-α), and increases the proliferative response per se, a reduction in oxidative stress and improvements in redox status may play a key role in the antifibrotic effects of icosabutate. A reduction in oxidative stress may also be involved in the significant reduction in proinflammatory genes regulated by the redox-sensitive transcription factor nuclear factor-κB, such as TNF-α. The ability of icosabutate to be rapidly excreted via the avoidance incorporation into complex lipids may play a key role in mediating the reduced oxidative stress.

For more information, refer to the icosabutate Investigator's Brochure.[1]

1.2 Coronavirus Disease 2019 Impacts

In March 2020, the Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2, was characterized as a pandemic by the World Health Organization (WHO). The COVID-19 pandemic has impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures; see Appendix G for details. The impacts of these implemented contingency measures on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the Clinical Study Report (CSR).

1.3 Non-Clinical Studies

Please see the Investigator's Brochure for detailed summaries of the nonclinical studies conducted with icosabutate.[1]

1.4 Clinical Studies

The completed clinical studies to date in the icosabutate clinical development program include 5 Phase 1 studies and 2 Phase 2 studies. The Phase 1 studies included a first-in-human pharmacokinetic (PK) and safety study in healthy volunteers (CTN4016 11101), a mass-balance study (CTN4016 14102), a drug-to-drug interaction study (CTN4016 14103), a thorough QTc study (NST-01), and a Phase 1b PK/PD and safety study in patients with mixed dyslipidemia (CTN4016 14104). The 2 Phase 2 studies evaluated treatment with icosabutate for 12 weeks in patients with high triglycerides (CTN4016 13201) and mixed dyslipidemia (CTN4016 13202).

These studies are supportive of the clinical development of icosabutate in patients with NASH without cirrhosis. Please refer to the Investigator's Brochure for additional detailed information on these studies. Additional clinical data not included in the Investigator's Brochure are summarized in the following sections.

1.4.1 Pre-Specified Interim Analysis of the Ongoing Phase 2b Study in Non-Cirrhotic Patients With NASH (Study NST-02)

1.4.1.1 Overview of interim analyses

A pre-specified interim analysis was performed in this ongoing Phase 2b study in patients with biopsy-confirmed NASH. This interim analysis was performed after 90 patients had randomized and completed 16 weeks of treatment. The purpose of this interim analysis was to evaluate safety as well as multiple non-invasive biomarkers relevant for NASH, fibrosis, metabolic syndrome, lipid metabolism, and cardiovascular risk. The individual patient disposition remains blinded to both the Investigators and the Sponsor but was unblinded to an independent Data Safety Monitoring Committee (DSMC) as part of their standard review. The baseline patient populations of the 90 patients in the interim analysis cohort were reflective of those enrolled into NASH clinical trials and generally well balanced across the treatment arms (Study NST-02 interim analysis; data on file).

1.4.1.2 Clinical pharmacodynamics

Rapid, sustained, and significant dose-dependent decreases were seen in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and alkaline phosphatase (ALP) at levels predictive of histologic improvement (see Table 1). Both doses showed significant reductions in N-terminal type 3 collagen propeptide (Pro-C3) and enhanced liver fibrosis (ELF) score (both total score and individual components) supporting an effect on fibrogenesis. High -sensitivity C-reactive protein (hsCRP) significantly decreased by 52% with 600 mg, in conjunction with improvements in glycemic control and key atherogenic lipoproteins. There were no changes in weight or body mass index (BMI), suggesting a treatment effect independent of weight loss. Liver fat content was unchanged with both doses, consistent with the icosabutate mechanism of action.

Table 1. Placebo-Adjusted Absolute Changes in Non-Invasive Biomarkers

Biomarker (Unit)	Icosabutate 300 mg (n=33)	Icosabutate 600 mg (n=35)
ALT (U/L)	-19*	-25.4*
AST (U/L)	-9.4#	-13.5#
GGT (U/L)	-16.9#	-28.6*
ALP (U/L)	-12.7*	-19.6*

Table 1. Placebo-Adjusted Absolute Changes in Non-Invasive Biomarkers (Continued)

Biomarker (Unit)	Icosabutate 300 mg (n=33)	Icosabutate 600 mg (n=35)
Bilirubin (mg/dL)	-0.0	-0.14#
Pro-C3 (ng/mL)	-4.5*	-4.6*
ELF	-0.4#	-0.6*
hsCRP (mg/L)	-1.2	-2.3#
HbA1c (%)	0.0	-0.3
HOMA-IR	-1.5	-2.1
LDL-C (mg/dL)	5.5	-3.9
HDL-C (mg/dL)	3.2#	2.3
Remnant-C (mg/dL)	-6.1#	-8.0*
ApoC3 (mg/dL)	-1.6#	-2.7*
TG (mg/dL)	-27.1#	-34.0#

* = p<0.001, # = p<0.05
ALP = alkaline phosphatase; ALT = alanine aminotransferase; ApoC3 = apolipoprotein C3; AST = aspartate aminotransferase; ELF = enhanced liver fibrosis; GGT = gamma glutamyl transferase; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein-cholesterol; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; Pro-C3 = N-terminal type 3 collagen propeptide; TG = triglyceride.
Source: Study NST-02 interim analysis (data on file)

1.4.1.3 Clinical safety

A safety review was performed of the 157 patients screened at the time of the Week 16 interim analysis with the treatment-emergent adverse events (TEAEs) presented in Table 2. There was no notable difference in the frequency, severity, or causality of the overall safety profile between placebo and either 300 mg or 600 mg of icosabutate for up to 16 weeks. The majority of TEAEs were mild to moderate in severity and generally comparable across the study arms. The treatment was well tolerated and comparable to placebo, with the exception of mild nausea (4.3%, 9.0%, and 21.3% in placebo, 300 mg, and 600 mg, respectively).

Table 2. Overview of TEAEs by Treatment Arm in Study NST-02

	Placebo (n=46)	Icosabutate 300 mg (n=46)	Icosabutate 600 mg (n=47)
Any TEAE (n [%])	37 (80.4%)	30 (65.2%)	37 (78.75%)
Maximum severity			
Grade 1 (n [%])	12 (26.1%)	7 (15.2%)	9 (19.1%)
Grade 2 (n [%])	24 (52.2%)	22 (47.8%)	20 (42.6%)
Grade 3 (n [%])	1 (2.2%)	1 (2.2%)	4 (8.5%)
Grade 4 (n [%])	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 5 (n [%])	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug-related TEAE (n [%])	7 (15.2%)	7 (15.2%)	8 (17.0%)
SAE (n [%])	1 (2.2%)	1 (2.2%)	3 (6.4%)
Drug-related SAE (n [%])	0 (0.0%)	0 (0.0%)	0 (0.0%)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Study NST-02 interim analysis (data on file)

No confirmed drug-induced liver injury, cardiovascular events, or worsening of diabetes were observed during the study period. Laboratory values remained stable or improved and there were no clinically relevant changes in vital signs or electrocardiograms (ECGs). No safety or tolerability signals of concern were observed during the study period as confirmed by an independent unblinded DSMC review. In summary, the safety and tolerability of icosabutate remains favorable and similar to that observed in other patient populations.

1.5 Risk/Benefit

Clinical studies conducted so far suggest that icosabutate is safe and well tolerated and confers clinically significant changes in triglycerides, atherogenic cholesterol, and other atherosclerotic risk markers such as apolipoprotein C3. The reduction in elevated liver enzymes seen in Phase 2 dyslipidemia studies, coupled with extensive animal models of NASH, suggest that icosabutate can be an important therapeutic option for the treatment of NASH.

In the clinical experience with icosabutate in patients with a lipid disorder, the overall incidence of adverse events throughout clinical studies has generally been low, and there have been no apparent treatment- or dose-related trends in the number of adverse events reported or the number of patients reporting adverse events. The most common adverse events seen in these patients were mild nausea and gastrointestinal bloating. Similarly, the interim analysis of the ongoing NST-02 study showed similar frequency and severity of overall adverse events in patients with NASH without cirrhosis. The most common adverse events, again, were gastrointestinal symptoms (other than an increase in mild gastrointestinal disturbance at supratherapeutic doses). There have been no other findings of clinical importance in the clinical laboratory evaluations, vital signs, 12-lead ECGs, telemetry, physical examinations, or body weight observed during the clinical studies. None of the nonclinical safety findings have been observed in the clinical studies, with no evidence of ophthalmic effects in human studies. A thorough QT study has demonstrated no effect of icosabutate on QT interval at supratherapeutic doses.

Based on the nonclinical and clinical experience to date, icosabutate has a favorable safety and tolerability profile with the potential for addressing common comorbid conditions in patients with NASH without cirrhosis. The potential benefits of icosabutate treatment in patients with NASH without cirrhosis outweigh any potential harm.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of different doses of NST-4016 on the resolution of NASH without worsening of fibrosis.

2.2 Secondary Objective

The secondary objective is to determine the safety and tolerability of NST-4016 in patients with NASH without cirrhosis.

3 STUDY DESCRIPTION

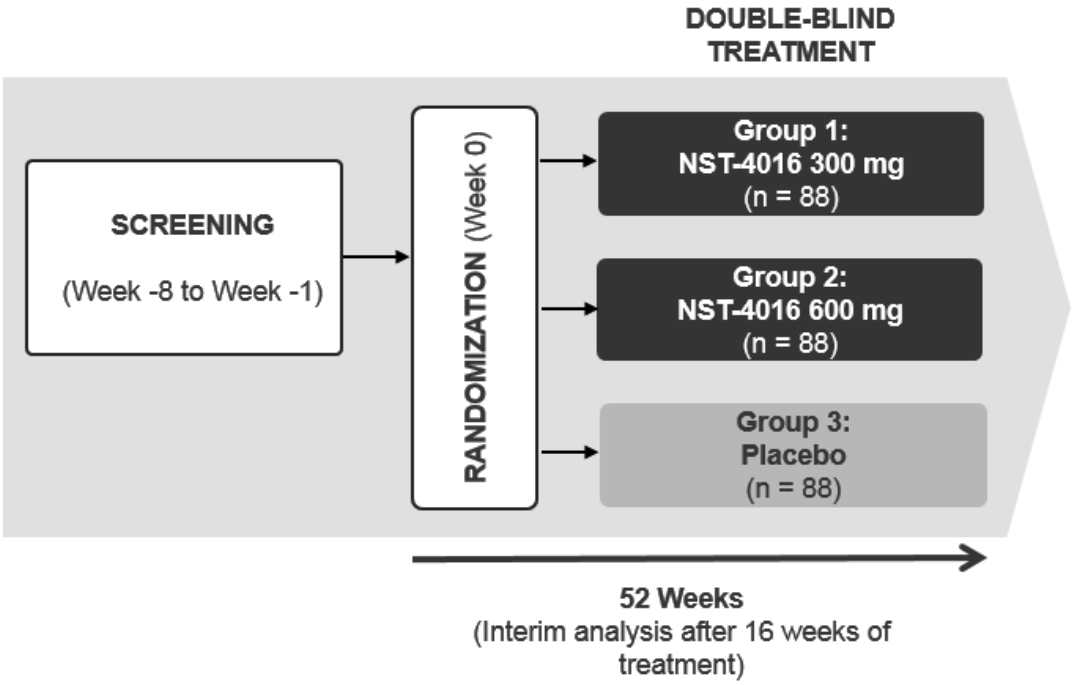
3.1 Summary of Study Design

This is a 62-week (including screening and follow-up), multicenter, randomized, double-blind, placebo-controlled, parallel-group study in male and female patients with a histological diagnosis of NASH.

The study includes a screening period, double-blind treatment period, and post-treatment follow-up. The Screening Visit will occur up to 8 weeks prior to randomization at Visit 2 (Week 0); more than 1 Screening Visit may be necessary to perform all required procedures. The double-blind treatment period will entail 52 weeks of dosing with study drug and will be followed by a Safety Follow-up Visit 2 weeks after the last dose of study drug.

Approximately 264 patients who meet the eligibility criteria will be randomized into 1 of 3 parallel treatment groups, each of which will contain approximately 88 patients. Patients in Group 1 will receive 300 mg NST-4016, patients in Group 2 will receive 600 mg NST-4016, and patients in Group 3 will receive placebo. Patients will be stratified by biopsy fibrosis score (2 levels: F1 versus F2 or F3). For a schematic of the study design, see Figure 1.

Figure 1. Study Design



Baseline assessments will include hepatic imaging (magnetic resonance imaging [MRI]-proton density-fat fraction [PDFF] and iron-corrected T1 [cT1]), liver biopsy, vital signs (blood pressure, pulse rate, and body temperature), physical examinations, laboratory evaluations (hematology, biochemistry, coagulation, and lipid panels and urinalysis), and 12-lead ECGs. Historical liver biopsy within 6 months of screening may be used for eligibility if evaluable histology slides are available for review by the central pathology reader. Historical liver biopsies obtained during the course of a prior investigational drug study must not be utilized if obtained within 3 months or 5 half-lives of the last dose of the prior investigational drug, whichever is longer. Patients who screen fail may be rescreened once. With the exception of MRI-PDFF, cT1, and liver biopsy,

baseline assessments will be collected at Visit 2 (Week 0, Day 0), prior to dosing; for MRI-PDFF, cT1, and liver biopsy, the assessments performed during screening will provide the baseline data.

Study drug dosing will begin at Visit 2 (Week 0, Day 0) and will continue daily for 52 weeks. During the 52-week treatment period, patients will return to the clinic for study visits every 1 to 3 months. The following assessments will occur at every study visit during the treatment period: adverse events, concomitant medications, body weight, vital signs, physical examinations, laboratory evaluations (hematology, biochemistry, coagulation, and lipid panels and urinalysis), and trough PK sampling. For a subset of patients (approximately 8 patients per group) at pre-identified sites, blood samples for analysis of additional PK parameters will also be collected predose and up to 24 hours postdose at Visit 2. In addition, hepatic imaging will be performed at Visit 5 (after 16 weeks of treatment) and Visit 9 (after 52 weeks of treatment).

Evaluation of liver inflammation and fibrosis biomarkers (Homeostatic Model Assessment for Insulin Resistance [HOMA-IR], hsCRP, Pro-C3, and ELF panel) will be performed at Visits 2, 5, and 9. Twelve-lead ECGs will be performed at Visits 2, 5, 7, and 9, and a liver biopsy will also be performed at Visit 9. Throughout the study, patients will be monitored for suspected drug-induced liver injury.

A Safety Follow-up Visit (Visit 10) will occur 14 days after the last dose of study drug to assess adverse events, concomitant medications, body weight, vital signs, physical examination findings, laboratory parameters, and 12-lead ECGs. Lipid parameters will be monitored throughout the follow-up period and will be managed by the Investigator.

Patients who discontinue early from the study for any reason prior to completion of the treatment period will be requested to return to the clinic for an Early Termination (ET) Visit as soon as possible after their last intake of study drug. Patients who discontinue early from the study for any reason after completion of the treatment period and before the Safety Follow-up Visit will be requested to return to the clinic for an ET Visit as soon as possible and no later than the planned Safety Follow-up Visit.

From screening through follow-up, the total study duration for each patient who completes the entire treatment period will be approximately 62 weeks. For a summary of procedures to be performed at each visit, refer to the Schedule of Procedures in Appendix A.

An external, independent DSMC will review all available unblinded preliminary safety and biomarker results per the DSMC Charter.

In addition, the following data was comprehensively reviewed during an interim analysis, which was performed after 90 patients had completed 16 weeks of treatment: ALT, AST, HOMA-IR, Pro-C3, ELF panel, MRI-PDFF, cT1, and lipid parameters.

3.1.1 Coronavirus Disease 2019 Contingency Measures

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures; see Appendix G for details. The impacts of these implemented contingency measures on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the CSR. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

3.2 Study Indication

The indication for this study is the treatment of patients with NASH without cirrhosis.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

A patient who meets all of the following criteria will be eligible to participate in the study:

1. Provides signed written informed consent and agrees to comply with the study protocol.
2. Is a male or female aged 18 to 75 years, inclusive.
3. Has a histological diagnosis of NASH without cirrhosis prior to study entry, as confirmed by either of the following:
   a. A historical liver biopsy within 6 months of screening (and has not received any NASH treatment since the biopsy). The histology slides from the historical biopsy must be evaluable and available for review by the central pathology reader. Historical liver biopsies obtained during the course of a prior investigational drug study must not be utilized if obtained within 3 months or 5 half-lives of the last dose of the prior investigational drug, whichever is longer.

      OR

   b. A contemporaneous liver biopsy during the screening period (Week -8 to Week -1). Patients without a historical biopsy must also have a FibroScan® vibration-controlled transient elastography (VCTE) measurement ≥8.5 kPa and a controlled attenuation parameter (CAP) for steatosis with cut-off values ≥300 dB/m at screening or a historical FibroScan (with eligible VCTE and CAP values) within 90 days of screening (prior to moving forward with the MRI-PDFF and subsequent liver biopsy).

      Note: Prior to performing a contemporaneous liver biopsy, patients must have 3 or more of the following metabolic risk factors:

      - Type 2 diabetes.
      - Elevated fasting glucose (≥100 mg/dL).
      - Elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg or on antihypertensive drug treatment).
      - Fasting high-density lipoprotein-cholesterol (<40 mg/dL in men or <50 mg/dL in women or on drug treatment).
      - Elevated fasting triglycerides (≥150 mg/dL but <300 mg/dL or on drug treatment).
      - Elevated waist circumference (>40 inches in men and >35 inches in women) present before performing the biopsy.
4. Has a Nonalcoholic Fatty Liver Disease Activity Score (NAS) ≥4, with a score of at least 1 in each component (steatosis, lobular inflammation, and ballooning), as per the central pathology reader.
5. Has a fibrosis score F1 to F3, inclusive (F1 capped at 20%), on liver biopsy as per the central pathology reader.
6. Has a PDFF ≥8% on MRI at screening, per the central imaging reader. The MRI-PDFF criteria will not apply if the patient has a qualifying historical liver biopsy.

7. Has ALT and AST <5 × upper limit of normal (ULN) and AST ≥20 U/L in men and ≥17 U/L for women upon entry into the study. A documented AST ≥30 U/L by a local laboratory within 60 days of screening will also be acceptable. The minimum AST criteria will not apply if the patient has a qualifying historical liver biopsy.
8. Has stable baseline liver enzymes, including serum ALT, AST, ALP, and total bilirubin values that are established by at least 2 samples demonstrating the following:
   a. Values of an enzyme in the 2 samples are within 1.5 × ULN ranges.

      OR

   b. If one of the enzyme levels is >1.5 × ULN, the variability between the 2 samples of ALT and AST does not exceed 50% and the variability between the 2 samples of ALP and total bilirubin does not exceed 30%.

   Notes:

   - The 2 samples need to be obtained 2 to 16 weeks apart.
   - One sample can be obtained from the patient's medical history and 1 sample can be obtained during the screening period, or both samples can be obtained during the screening period.
   - A third sample may be collected if the variability between the first 2 samples exceeds the limits in Inclusion Criterion 8b and one of these values is deemed spurious.
9. Has no other cause of chronic liver disease (eg, autoimmune disorder, alcoholic liver disease, drug-induced liver disease, primary biliary cholangitis, primary sclerosing cholangitis, hepatitis B virus, hepatitis C virus [HCV], Wilson's disease, α-1-antitrypsin deficiency, hemochromatosis) and has not had a liver transplant.
10. If the patient has type 2 diabetes mellitus (T2DM), he/she has stable T2DM, defined as hemoglobin A1c (HbA1c) ≤9.5% at screening and no new symptoms associated with decompensated diabetes in the previous 3 months.
11. Has a stable body weight, defined by no more than a 5% loss in initial body weight for at least 3 months or since the liver biopsy was performed, whichever is longer.
12. Has a BMI ≥25 kg/m^2 and ≤50 kg/m^2.
13. Is willing to undergo a liver biopsy after 52 weeks of treatment.
14. Is not of childbearing potential or, if of childbearing potential, is not pregnant as confirmed by a negative serum human chorionic gonadotropin (hCG) test at screening and is not planning a pregnancy during the course of the study.

    Note: A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile (permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). A postmenopausal state is defined as no menses for ≥12 consecutive months without an alternative medical cause. A follicle-stimulating hormone (FSH) level in the postmenopausal range will be used to confirm a postmenopausal state in women ≤55 years of age.

15. Male and female patients of childbearing potential must agree to use a dual method of contraception (a highly effective method of contraception in conjunction with a barrier contraception) consistently and correctly from the first dose of study drug until 90 days after the last dose of study drug. Highly effective methods of contraception are those that result in a failure rate of less than 1% per year when used consistently and correctly and include the following: hormonal intrauterine devices; hormonal contraceptives (oral birth control pills, depo, patch, or injectable); male sterilization performed more than 6 months prior to screening; and complete abstinence from sexual intercourse (if this is the patient's usual and preferred lifestyle). Barrier methods of contraception include male or female condoms used in combination with a separate spermicide product (eg, foam, gel, film, cream, or suppository).
16. Male patients must agree to abstain from sperm donation from the first dose of study drug until 90 days after the last dose of study drug.

4.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in the study:

1. Has a known history of alcohol abuse or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [1 unit of alcohol is equivalent to a half pint of beer {285 mL}, 1 measure of spirits {25 mL}, or 1 glass of wine {125 mL}]). Alcohol abuse will be defined as having an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score of ≥3 points for men and women AND a full Alcohol Use Disorders Identification Test (AUDIT) score of ≥8 points at screening.

   Note: Only patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
2. Has had bariatric surgery within the past 5 years or has bariatric surgery planned to occur during the study.
3. Has significant systemic or major illnesses other than liver disease, including pulmonary disease, renal failure, organ transplantation, serious psychiatric disease, or malignancy that, in the opinion of the Investigator, would preclude treatment with NST-4016 or confound the study results. This would include any malignancy under evaluation, or diagnosed and/or treated within the past 2 years except for squamous or non-invasive basal skin cell or cervical carcinoma in-situ.
4. Has a recent (within 6 months) history of cardiac dysrhythmias and/or cardiovascular disease, including congestive heart failure (class C and D of the American Heart Association [AHA]), unstable coronary artery disease, cerebrovascular disease, or myocardial infarction.
5. Has uncontrolled arterial hypertension.
6. Has hepatitis B surface antigen >0, HCV antibody and HCV polymerase chain reaction (PCR) >0 (HCV PCR only required for patients who test positive for HCV antibody; patients with a confirmed history of HCV infection can be included if HCV PCR has been negative for at least the last 2 years), or human immunodeficiency virus (HIV) infection.
7. Has type 1 diabetes mellitus.
8. Has diabetic ketoacidosis.

9. Has a history of liver decompensation, such as ascites, esophageal varices, and hepatic encephalopathy.
10. Has any of the following exclusionary laboratory results upon entry into the study:
    a. Hemoglobin ≤11 g/dL for females and ≤12 g/dL for males.
    b. White blood cell count ≤2.5 K/μL.
    c. Neutrophil count ≤1.5 K/μL.
    d. Platelet count ≤150 K/μL.
    e. Total bilirubin ≥1.3 mg/dL. Patients with total bilirubin ≥1.3 mg/dL can be included if direct bilirubin is within normal ranges in the setting of Gilbert's syndrome.
    f. Albumin <3.6 g/L.
    g. International Normalized Ratio ≥1.3, unless due to anti-coagulant therapy.
    h. Thyroid-stimulating hormone >1.5 × ULN.
    i. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
    j. Fasting triglyceride level >300 mg/dL.

    Note: Repeat testing may be performed in consultation with the Medical Monitor if any of the above laboratory parameters are outside the specified ranges.
11. Has a hemostasis disorder.
12. Has any contraindication to liver biopsy or MRI.
13. Has any clinically significant ECG abnormality at screening.
14. Has participated in any other investigational drug study within the previous 3 months or 5 half-lives of the last dose of the investigational drug, whichever is longer.
15. Has a known hypersensitivity to any of the ingredients or excipients of the study drug.
16. Has used any drug known to produce hepatic steatosis, including systemic corticosteroids, methotrexate, tetracycline, amiodarone, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid, for more than 2 weeks in the 6 months prior to screening. Local corticosteroid injection for musculoskeletal disorders is permitted, including epidural corticosteroid administration.
17. Is unable to comply with the following concomitant medication restrictions:
    a. Lipid-lowering therapies must be stable for ≥3 months at screening. Fish oil and other omega-3 compounds must also be stable for ≥3 months at screening if the dose is ≥1000 mg per day.
    b. Antidiabetic drugs, including insulin regimens, must be stable for ≥3 months at screening, with the exception of sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) agonists, which must be stable for ≥6 months at screening.

c. No vitamin E >400 U/d, pioglitazone, obeticholic acid, or antiobesity drugs for 3 months prior to screening or since the liver biopsy, whichever is longer.

18. Has any other condition that, in the opinion of the Investigator, would impede competence or compliance or possibly hinder completion of the study.
19. Uses any prohibited medications (see Section 5.6) or any concomitant medications used to treat an exclusionary medical condition.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality (including meeting any of the suspected drug-induced liver injury criteria as described in the Drug-Induced Liver Injury Monitoring Plan in Appendix E), intercurrent illness, or other medical condition that is considered related to the study drug or indicates to the Investigator that continued participation is not in the best interest of the patient
- Pregnancy
- Requirement of prohibited concomitant medication after consultation with the Medical Monitor
- Patient failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the End of Treatment Visit (Visit 9, Week 52). The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records. A minimum of 3 attempts to contact the patient must be made and documented prior to declaring the patient lost to follow-up.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Approximately 264 eligible patients with NASH will be randomized into 1 of 3 parallel treatment groups (stratified by biopsy fibrosis score), each of which will contain approximately 88 patients, as outlined in Table 3.

Table 3. Study Treatment Groups and Dosing Regimens

Treatment Group	Dosing Regimen [1]
Group 1: 300 mg NST-4016	1 capsule (300 mg) NST-4016 and 1 capsule matching placebo
Group 2: 600 mg NST-4016	2 capsules (300 mg each) NST-4016
Group 3: placebo	2 capsules matching placebo

1. Patients will take 2 capsules in the morning with water once daily (at approximately the same time each day) for 52 weeks. Study drug can be taken in the fed or fasted state.

5.2 Rationale for Dosing

The maximum dose selected for this study (600 mg) was previously administered for 12 weeks daily in patients with hypertriglyceridemia or mixed dyslipidemia and demonstrated statistically significant and clinically meaningful reductions in triglycerides and cholesterol and was shown to be safe and well tolerated. Single ascending doses >600 mg (up to 2800 mg) resulted in increasing gastrointestinal side effects, which were mainly mild. The low dose selected for this study (300 mg) demonstrated significant reductions in triglycerides and cholesterol, although not as notable as the effects seen with 600 mg dosing. These 2 doses are expected to provide evidence of a dose-response relationship in patients with NASH. Once-daily dosing is consistent with the sustained PD effects seen on lipids in repeat-dose studies.

5.3 Randomization and Blinding

This study follows a randomized, double-blind, placebo-controlled design. Patients will be randomized via the Interactive Response Technology (IRT) system to 1 of 3 parallel treatment groups at Visit 2 (Week 0) in a 1:1:1 ratio. Patients will be stratified by biopsy fibrosis score (2 levels: F1 versus F2 or F3). Randomization information will be concealed from the Investigators and the patients until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment.

Both NST-4016 and placebo will be provided as capsules for oral administration and will be identical in appearance.

5.4 Breaking the Blind

Until formal conclusion of the study, patients, Investigators, and all site study personnel will remain blinded to treatment allocation, except in the event of a medical emergency that necessitates unblinding. In the event of a medical emergency where knowledge of the patient's treatment assignment would influence the patient's clinical care, the site will be able to unblind the patient via the IRT system. The site should consult the study Medical Monitor prior to unblinding if at all possible without putting the patient's safety at risk. In the case of unblinding, the IRT system will send a blinded notification to study team members to let them know that a patient was unblinded.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The drug product is presented as red, oblong-shaped, soft gelatin capsules. The formulation is designed as 300 mg icosabutate (drug substance) in Self-Emulsifying Drug Delivery System (SEDDS). In general, a SEDDS formulation is a mixture of oils and surfactants, which emulsify in aqueous media under conditions of gentle agitation and digestive motility that would be encountered in the stomach and gastrointestinal tract. The use of a self-emulsifying formulation is proposed to increase the bioavailability of drugs with poor water solubility. The formulation contains 300 mg icosabutate formulated in polysorbate 20 and triglycerides medium-chain, with 3-tert-butyl-4-hydroxyanisole added in order to prevent oxidation of the drug substance.

The production of the capsules is carried out under nitrogen. The capsules are packaged as bulk in double polyethylene bags inside a cardboard box. The soft gelatin capsules are packed for patients in high-density polyethylene bottles with a tamper-proof polypropylene screw cap.

5.5.2 Study Drug Preparation and Dispensing

Study drug will be dispensed as 300 mg capsules for oral administration at Visits 2 to 8 by blinded site personnel. Patients will receive enough study drug to last until the next study visit.

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to study drug dispensation specific to situations where COVID-19 is impacting study conduct. See Appendix G for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

5.5.3 Study Drug Administration

All patients will take 2 capsules of study drug (either 300 mg NST-4016 and/or matching placebo) orally in the morning with water once daily for 52 weeks. In the event that the Visit 9 biopsy is delayed, patients will continue to administer study drug daily until the biopsy occurs, for up to 30 days after the originally projected Visit 9 date.

Patients should take study drug at approximately the same time each day. Study drug can be taken in the fed or fasted state.

On study visit days, patients should take their daily dose of study drug at the clinical site to accommodate predose trough PK sampling.

5.5.4 Treatment Compliance

The quantity of study drug dispensed to and returned by the patient will be counted by site personnel and verified by the Clinical Research Associate (CRA) monitoring the study. All discrepancies in drug accountability should be explained and documented (missed dose, lost capsule, overdose, etc). If the patient is not compliant with study drug intake, the Investigator should discuss this with the patient.

If study drug compliance drops below 80% or surpasses 100% at any given time during the treatment period, the Investigator or designee should discuss compliance with the patient and counsel the patient appropriately. Noncompliance includes missed doses in addition to taking the

wrong dose. The Investigator must continually encourage compliance with the study drug and with the study procedures.

5.5.5 Storage and Accountability

The study drug should be stored refrigerated at 2°C to 8°C for up to 18 months and protected from light. The study drug may be kept at room temperature (not exceeding 25°C) by the patients between study visits for a maximum of 3 months. In case of longer excursions at 15°C to 25°C, the study drug should not be used but returned to site for replacement with new study drug. The study drug must not be frozen.

At the completion of the study, all used and unused supplies should be accounted for, and any unused study drug should be returned to the clinical site for destruction or for return to the distribution site (or designee) for destruction.

5.6 Prior and Concomitant Medications and/or Procedures

Unless medically warranted, all concomitant medications should remain stable from screening through the Safety Follow-up Visit (Visit 10). Throughout the duration of the study, patients should not introduce changes to their usual diet (including dietary supplements) or lifestyle.

5.6.1 Excluded Medications and/or Procedures

Excluded medications and procedures include the following:

- Any drug known to produce hepatic steatosis, including systemic corticosteroids, methotrexate, tetracycline, amiodarone, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid, for more than 2 weeks in the 6 months prior to screening. Local corticosteroid injection for musculoskeletal disorders is permitted, including epidural corticosteroid administration.
- Vitamin E >400 U/d, pioglitazone, obeticholic acid, or antiobesity drugs within 3 months prior to screening or since the historical liver biopsy (if applicable), whichever is longer.
- CYP3A or CYP2C19 substrates that have a narrow therapeutic index, as exposure may be reduced.
- Strong inhibitors of CYP2C8, CYP2C9, or CYP2C19.
- Bariatric surgery within the past 5 years or bariatric surgery planned to occur during the study.
- Participation in any other investigational drug study within the previous 3 months or 5 half-lives of the last dose of the investigational drug, whichever is longer.

5.6.2 Restricted Medications and/or Procedures

Patients receiving lipid-lowering treatments need to be on stable therapy for at least 3 months prior to screening and must agree to remain on a stable regimen for their entire participation in the study unless the patient is unable to achieve adequate control with current therapy. Patients may switch drugs within a class prior to screening if the lipids remain controlled (as assessed 30 days after the switch), the drug is well tolerated, and there is no exclusionary drug interaction.

Fish oil and other omega-3 compounds must also be stable for ≥3 months at screening if the dose is ≥1000 mg per day.

Throughout study treatment, laboratory alerts will be in place to notify the Investigator of low-density lipoprotein-cholesterol (LDL-C) values. If LDL-C increases from baseline by 10 mg/dL and is >ULN on 2 consecutive visits, additional treatment (eg, initiation of statin therapy or an increase in the statin dose for patients who are already on treatment) may be introduced according to the 2018 AHA/American College of Cardiology (ACC) Guideline on the Management of Blood Cholesterol,[2] after discussion with the Sponsor's Medical Monitor.

Throughout the study, it is recommended that a patient's LDL-C is managed in accordance with the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol. The 2018 AHA/ACC Guideline on the Management of Blood Cholesterol recommends personalized risk assessments and new cholesterol-lowering drug options for people at the highest risk for cardiovascular disease. The guideline provides treatment algorithms for Primary Atherosclerotic Cardiovascular Disease (ASCVD) prevention and Secondary ASCVD prevention. See Appendix F for links to the full and abbreviated versions of the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol.

In this study, it is recommended that a patient's LDL-C is managed with a statin, when necessary, in accordance with the treatment algorithm outlined in the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol. In addition, Investigators should identify patients who are at "Very High Risk of Future ASCVD Events" who may benefit from additional LDL-C lowering therapy. Patients with "Very High Risk of Future ASCVD Events" include those with multiple major ASCVD events in the past or 1 major ASCVD event and multiple high-risk conditions as defined below:

- Major ASCVD events include the following:
  - Recent acute coronary syndrome (within the past 12 months)
  - History of myocardial infarction (other than recent acute coronary syndrome event listed above)
  - History of ischemic stroke
  - Symptomatic peripheral arterial disease (history of claudication with ankle brachial index)
- High-risk conditions include the following:
  - Age ≥65 years
  - Heterozygous familial hypercholesterolemia
  - History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
  - Diabetes mellitus
  - Hypertension
  - Chronic kidney disease (eGFR 15 to 59 mL/min/1.73 m^2)
  - Current smoking

- Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
- History of congestive heart failure

In certain circumstances as outlined in AHA/ACC treatment algorithm, Investigators should consider other cholesterol-lowering medications along with statins. For example, patients with a history of myocardial infarction or ischemic stroke, who have high-risk conditions as outlined above. A stepwise approach should be used. If a patient is already on a maximal dose statin (eg, rosuvastatin 40 mg) and has LDL-C ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe is a reasonable step. If that combination is not successful, then the addition of a proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor should be considered. However, if a patient is unable able to tolerate a maximal dose of statin, then ezetimibe can be added. In addition, for patients who are unable to take statins (eg, due to poor tolerability or adverse effects), then adding ezetimibe or a PCSK9 inhibitor such as evolocumab or alirocumab would be a reasonable approach.

Lipid parameters will be monitored throughout the follow-up period and any lipid-lowering treatment started during the study should be reviewed during the follow-up period and adjusted or discontinued in accordance with the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol.

Patients with T2DM should be on a stable dose of antidiabetic medication, including insulin regimens, for at least 3 months prior to screening (with the exception of SGLT2 inhibitors and GLP-1 agonists, which must be stable for ≥6 months at screening). Patients may switch drugs within a class prior to screening if the fasting plasma glucose (FPG) and HbA1c remain controlled (as assessed 30 days after the switch), the drug is well tolerated, and there is no exclusionary drug interaction. Patients must agree to remain on a stable regimen for their entire participation in the study unless at the Investigator's discretion and according to the following rules:

- In case of confirmed FPG/HbA1c above the threshold value, defined as FPG >270 mg/dL (15.0 mmol/L) and HbA1c >9% (for patients with baseline HbA1c <8%) and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥8% and ≤9.5%), the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and that:
  - Plasma glucose was measured in the fasting condition.
  - Absence of intercurrent disease that may jeopardize glycemic control. In case of an emergency (eg, surgery, infection), the Investigator can take appropriate measures for glycemic control.
  - Compliance to treatment is appropriate.
  - Compliance to diet and lifestyle is appropriate.

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event/concomitant medication forms on of the eCRF).
- Stress to the patient the need to be compliant to treatment.
- Stress to the patient the need to be compliant to diet and lifestyle recommendations.

An FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor's Medical Monitor.

5.6.3 Documentation of Prior and Concomitant Medication Use

All prior and concomitant medications will be documented in the eCRF. Prior medications include any medication taken within 6 months prior to screening. Concomitant medications include any medication taken on or after the date the patient signs informed consent. Any changes to concomitant medication dosing during the study will be captured in the eCRF and closely monitored.

6 STUDY PROCEDURES

A ±7-day window is acceptable for all visits during the treatment period, except for Visit 3 and Visit 10 (Week 4 and Week 54, respectively), when the window is ±5 days.

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to visit schedules and procedures specific to situations where COVID-19 is impacting study conduct. See Appendix G for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

6.1 Informed Consent

Written informed consent for the study will be obtained from all patients before any protocol specific procedures are performed. For a subset of patients (approximately 8 patients per group) at pre-identified sites, additional consent will be required for those patients who consent to also undergo intensive PK sampling.

6.2 Screening Visit (Visit 1, Week -8 to Week -1)

For patients without a historical biopsy (ie, if the patient does not have evaluable histology slides from a liver biopsy performed in the previous 6 months available for review by the central pathology reader), FibroScan, MRI-PDFF, and liver biopsy procedures should be conducted in the following order: 1) FibroScan assessment (if the patient does not have a historical FibroScan with eligible VCTE and CAP values within 90 days of screening); 2) MRI-PDFF (if FibroScan values [VCTE and CAP] are within eligibility range); and 3) liver biopsy (if MRI-PDFF is within eligibility range).

The following procedures will be performed at the Screening Visit (Visit 1); more than 1 visit may be necessary to complete all required procedures. Patients who screen fail may be rescreened once.

- Obtain informed consent.
- Evaluate inclusion/exclusion criteria.
- Obtain demographics and medical history.
- Record prior medications (any medication taken within 6 months prior to screening) and concomitant medications.
- Measure height and body weight and calculate BMI.
- Perform complete physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test. Patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT at screening and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.

- Collect fasting blood sample for the following:
  - Viral serology (hepatitis B virus, HCV, and HIV).
  - Hematology, biochemistry, coagulation, and lipid panels. If a patient has a qualifying historical biopsy, the required AST levels (AST ≥20 U/L in men and ≥17 U/L in women by central laboratory or AST ≥30 U/L by a local laboratory within 60 days of screening; see Inclusion Criterion 7) will not be applied.
  - Serum pregnancy test (only for women of childbearing potential).
  - FSH test (only for women ≤55 years of age, to confirm postmenopausal state).
- Collect urine sample for urinalysis.
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Perform FibroScan (if the patient does not have a historical FibroScan with eligible VCTE and CAP values within 90 days of screening) for patients without historical biopsy.
- Perform MRI-PDFF if FibroScan values (VCTE and CAP) are within eligibility range (only for patients without historical biopsy) or the patient is eligible based on the historical biopsy. If the patient is eligible based on a historical biopsy, the MRI-PDFF procedure should be performed but the eligibility criterion of liver fat content ≥8% will not be applied (see Inclusion Criterion 6).
- Perform liver biopsy (only for patients without historical biopsy) if the FibroScan and MRI-PDFF values are within eligibility range.
- Assess adverse events.

6.3 Treatment Period – Visit 2 to Visit 9 (Week 0 to Week 52)

All visits in the treatment period have a visit window of ±7 days, with the exception of Visit 3, which has a visit window of ±5 days.

6.3.1 Visit 2 (Week 0)

The following procedures will be performed at Visit 2 (Week 0):

- Reassess inclusion/exclusion criteria prior to dosing to ensure no changes in eligibility have occurred since screening.
- Obtain medical history.
- Record concomitant medications.
- Measure body weight and calculate BMI (using height at screening).
- Calculate iron-corrected T1 values using screening MRI.
- Perform complete physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.

- Collect fasting blood sample for the following:
  - Hematology, biochemistry, coagulation, and lipid panels.
  - Lipoprotein particle size.
  - Serum pregnancy test (only for women of childbearing potential).
  - Biomarkers (HOMA-IR, hsCRP, Pro-C3, and ELF panel).
  - Lipidomic analyses (in a subgroup of patients, even if using existing samples).
- Collect urine sample for urinalysis.
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Randomize eligible patients prior to dosing.
- Assess adverse events.
- Collect a predose PK blood sample.

  Note: For those patients participating in the intensive PK subset, collect PK blood samples in relation to the first dose of study drug at the following timepoints: predose (within 1 hour prior to the first dose), followed by 1, 2, 3, 4, 6, and 8 hours postdose (±10 minutes) at Visit 2 (Day 0) and 24 hours postdose (±1 hour, but prior to the second dose of study drug on Day 1).
- Administer first dose of study drug on site.
- Dispense study drug and provide dosing instructions for off-site dosing until next study visit.

6.3.2 Visit 3 (Week 4)

The following procedures will be performed at Visit 3 (Week 4):

- Record concomitant medications.
- Measure body weight.
- Perform abbreviated physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for hematology, biochemistry, coagulation, and lipid panels.
- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).
- Assess adverse events.
- Collect a predose PK blood sample.
- Collect returned and used/unused study drug and assess compliance.

- Administer study drug on site.
- Dispense new study drug for dosing until the next study visit.

6.3.3 Visit 4 (Week 10)

The following procedures will be performed at Visit 4 (Week 10):

- Record concomitant medications.
- Measure body weight.
- Perform abbreviated physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for hematology, biochemistry, coagulation, and lipid panels.
- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).
- Assess adverse events.
- Collect a predose PK blood sample.
- Collect returned and used/unused study drug and assess compliance.
- Administer study drug on site.
- Dispense new study drug for dosing until the next study visit.

6.3.4 Visit 5 (Week 16)

The following procedures will be performed at Visit 5 (Week 16):

- Record concomitant medications.
- Measure body weight.
- Perform abbreviated physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for the following:
  - Hematology, biochemistry, coagulation, and lipid panels.
  - Lipoprotein particle size.
  - Biomarkers (HOMA-IR, hsCRP, Pro-C3, and ELF panel).
- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).

- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Perform MRI-PDFF and cT1 imaging.
- Assess adverse events.
- Collect a predose PK blood sample.
- Collect returned and used/unused study drug and assess compliance.
- Administer study drug on site.
- Dispense new study drug for dosing until the next study visit.

6.3.5 Visit 6 (Week 24)

The following procedures will be performed at Visit 6 (Week 24):

- Record concomitant medications.
- Measure body weight.
- Perform abbreviated physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for hematology, biochemistry, coagulation, and lipid panels.
- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).
- Assess adverse events.
- Collect a predose PK blood sample.
- Collect returned and used/unused study drug and assess compliance.
- Administer study drug on site.
- Dispense new study drug for dosing until the next study visit.

6.3.6 Visit 7 (Week 32)

The following procedures will be performed at Visit 7 (Week 32):

- Record concomitant medications.
- Measure body weight.
- Perform abbreviated physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for hematology, biochemistry, coagulation, and lipid panels.

- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Assess adverse events.
- Collect a predose PK blood sample.
- Collect returned and used/unused study drug and assess compliance.
- Administer study drug on site.
- Dispense new study drug for dosing until the next study visit.

6.3.7 Visit 8 (Week 40)

The following procedures will be performed at Visit 8 (Week 40):

- Record concomitant medications.
- Measure body weight.
- Perform abbreviated physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for hematology, biochemistry, coagulation, and lipid panels.
- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).
- Assess adverse events.
- Collect a predose PK blood sample.
- Collect returned and used/unused study drug and assess compliance.
- Administer study drug on site.
- Dispense new study drug for dosing until the next study visit.

6.3.8 Visit 9 (Week 52)

The following procedures will be performed at Visit 9 (Week 52):

- Record concomitant medications.
- Measure body weight.
- Perform complete physical examination.

- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for the following:
  - Hematology, biochemistry, coagulation, and lipid panels.
  - Lipoprotein particle size.
  - Biomarkers (HOMA-IR, hsCRP, Pro-C3, and ELF panel).
  - Lipidomic analyses (in a subgroup of patients).
- Collect urine sample for the following:
  - Urinalysis.
  - Urine pregnancy test (only for women of childbearing potential).
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Perform MRI-PDFF and cT1 imaging.
- Perform liver biopsy for analyses (including lipidomics in a subset of patients).
- Assess adverse events.
- Collect a PK blood sample.
- Collect returned and used/unused study drug and assess compliance.

6.4 Safety Follow-up Visit (Visit 10, Week 54)

The Safety Follow-up Visit has a visit window of ±5 days. The following procedures will be performed at the Safety Follow-up Visit (Visit 10, Week 54):

- Record concomitant medications.
- Measure body weight.
- Perform complete physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for the following:
  - Hematology, biochemistry, coagulation, and lipid panels.
  - Serum pregnancy test (only for women of childbearing potential).
- Collect urine sample for urinalysis.
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Assess adverse events.

6.5 Early Termination Visit and Withdrawal Procedures

The end of treatment for patients completing the study is Visit 9 (Week 52). For patients who are withdrawn from the study prior to completion, all Visit 9 procedures will be performed at an ET Visit. Liver biopsy at ET will only be performed for patients who have been on study drug for at least 6 months.

Patients who discontinue early from the study for any reason prior to completion of the treatment period will be requested to return to the clinic for an ET Visit as soon as possible after their last intake of study drug.

If a patient discontinues early from the study for any reason after completion of the treatment period but before the Safety Follow-up Visit, sites should make every attempt to bring the patient into the site for the Safety Follow-up Visit.

The following procedures will be performed at the ET Visit:

- Record concomitant medications.
- Measure body weight.
- Perform complete physical examination.
- Collect vital signs (blood pressure [3 readings], pulse rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Collect fasting blood sample for the following:
    - Hematology, biochemistry, coagulation, and lipid panels.
    - Lipoprotein particle size.
    - Biomarkers (HOMA-IR, hsCRP, Pro-C3, and ELF panel).
    - Serum pregnancy test (only for women of childbearing potential).
    - Lipidomic analyses (in a subgroup of patients).
- Collect urine sample for urinalysis.
- Perform 12-lead ECG after the patient has been resting in the supine position for at least 10 minutes.
- Perform MRI-PDFF and cT1 imaging.
- Perform liver biopsy (if patient has been on study drug for at least 6 months) for analyses (including lipidomics in a subset of patients).
- Assess adverse events.
- Collect a PK blood sample.
- Collect returned and used/unused study drug and assess compliance.

7 EFFICACY ASSESSMENTS

7.1 Efficacy Variables

7.1.1 Primary Efficacy Variable

The primary efficacy parameter is the percentage of patients with resolution of NASH, defined as disappearance of ballooning (score = 0) with lobular inflammation score 0 or 1, with no worsening of fibrosis.

7.1.2 Secondary Efficacy Variables

The secondary efficacy parameters include the following:

- Change from baseline in NAS
- Changes in individual histological scores for steatosis, ballooning, inflammation, and fibrosis
- Changes in the liver enzymes AST, ALT, GGT, and bilirubin
- Changes in the imaging parameters MRI-PDFF and cT1
- Changes in the inflammation marker hsCRP
- Changes in the fibrosis activity markers Pro-C3 and ELF panel
- Changes in HOMA-IR, a measure of insulin resistance and metabolic status

7.1.3 Exploratory Biomarker Analysis

The exploratory parameters include the following (in a subgroup of patients):

- Profile and characterization of lipid species on End of Treatment Visit liver biopsy
- Profile and characterization of lipid species on baseline and End of Treatment serum samples

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time the patient signs the informed consent form (ICF) until Visit 10 (Week 54) or the ET Visit (if applicable). Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment. Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at screening changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event and will also categorize each adverse event as to its potential relationship to study drug.

The Investigator will assess all adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grading system.

Assessment of severity

The severity of all adverse events should be graded according to the CTCAE. For those adverse event terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death related to the adverse event

Causality assessment

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence of predefined adverse events of special interest (AESIs) throughout the patient's participation in this study.

Events of suspected drug-induced liver injury will be monitored as AESIs during this study. During the course of the study, additional AESIs may be identified by the Sponsor.

The Investigator will assess and record in detail any additional information on AESIs on an SAE form (whether or not the event meets seriousness criteria in Section 8.2), to be submitted within 24 hours of awareness of the event. Adverse events of special interest must be recorded on the eCRF.

8.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.

  Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations.

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing the ICF, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly/birth defect.

- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last dose of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to the Medpace Clinical Safety or Sponsor designee.

To report the SAE, complete the SAE form electronically in the Electronic Data Capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at Medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax/email. If it

is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period (ie, prior to the Safety Follow-up Visit), the Investigator is to stop dosing with study drug(s) immediately, and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the Food and Drug Administration as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal products.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the study drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where a medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of patients missing doses of investigational product are not considered reportable as medication errors.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All adverse events associated with these Special Situation Report forms should be reported as adverse events or SAEs, as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

8.7 Clinical Laboratory Evaluations

Clinical safety laboratory parameters will be measured or calculated at all study visits (see Appendix A). Fasting hematology, biochemistry, coagulation, and lipid panels and urinalysis parameters will be evaluated at all study visits. Further analysis of urine sediment or urine microscopy will be performed if there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite. Although lipid parameters will be evaluated at every visit, lipoprotein particle size will be assessed only at baseline, Week 16, and at the end of treatment (Week 52/ET). Lipid parameters will be monitored throughout the follow-up period and any lipid-lowering treatment started during the study should be reviewed during the follow-up period and adjusted or discontinued in accordance with the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol.[2] See Appendix F for links to the full and abbreviated versions

of the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol. See Appendix B for a complete list of laboratory analytes.

For women of childbearing potential, a serum hCG test will be performed at screening, Week 0, and at study exit (whether at the Safety Follow-up or ET Visit). Urine hCG testing will be performed at all other visits. If a urine hCG test is positive, pregnancy will be confirmed by a serum hCG test. Follicle-stimulating hormone level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.

Samples will be collected for viral serology at screening to confirm patients are negative for hepatitis B virus, HCV (patients with a confirmed history of HCV infection can be included if HCV PCR is negative for at least the last 2 years), and HIV infection.

Blood sampling procedures, including information on blood volume, collection tubes, sample processing, storage, and shipping are provided in the Laboratory Manual. Where necessary, local laboratory testing will be acceptable to monitor events of suspected drug-induced liver injury.

Technical details on laboratory parameters (methods and commercial kit[s]) will be specified in the Laboratory Manual.

8.8 Vital Signs

Vital signs will be collected at every study visit and will include blood pressure, pulse rate, and body temperature, and will be performed with the patient in the sitting position after 5 minutes of rest and before any blood draws. Three replicate blood pressure readings will be taken at each visit.

8.9 Electrocardiograms

Single 12-lead ECGs will be performed at screening; Visits 2, 5, 7, and 9; and at study exit (whether at the Safety Follow-up or ET Visit). Single 12-lead ECGs will be performed after the patient has been resting in the supine position for at least 10 minutes. In case of evident bad quality of the tracing (eg, muscle tremor), the ECG will be repeated. QTcF will be measured.

8.10 Physical Examinations

Full physical examinations (including general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological systems; mental status; and extremities) will be performed at screening; Visits 2 and 9; and at study exit (whether at the Safety Follow-up or ET Visit). Abbreviated physical examinations will be performed at all other visits. Abbreviated physical examinations should be targeted based on Investigator discretion and interval history.

8.11 Imaging Assessments

Hepatic imaging by MRI will be performed using a standardized central imaging protocol provided to each site and validated by the central imaging reader.

Images will be provided to the central imaging reader in order to assess the following parameters:

- MRI-PDFF: a chemical shift-based method to assess for water-fat separation. This has been shown to correspond to histological measures of steatosis.
- cT1: a measure of free-water content in tissue. This has been shown to increase in inflammation and fibrosis, when corrected for hepatic iron.

Hepatic imaging will be performed at screening, Visit 5, and Visit 9 (or the ET Visit, if applicable). The MRI performed during screening will provide the baseline data for MRI-PDFF and cT1; however, baseline cT1 will be calculated at Visit 2, only after the patient is randomized.

8.12 Liver Biopsies

Liver biopsies will be performed at screening and Visit 9 (or the ET Visit, if applicable and the patient has been on study drug for at least 6 months). Assessment of the tissue collected will be performed by a blinded central pathology reader. In addition, in a subgroup of patients, the tissue collected at the End of Treatment Visit (Visit 9) will be analyzed by a central laboratory (OWL) for lipidomic analyses. Further details on biopsy collection, processing, storage, and shipping and the central review process are provided in the laboratory manual and biopsy review charter.

8.12.1 Nonalcoholic Fatty Liver Disease Activity Score

The NAS was developed as a tool to measure clinical disease changes by scoring the features of NASH during therapeutic trials.

The total NAS represents the sum of scores for steatosis, lobular inflammation, and ballooning, and ranges from 0 to 8.

The NAS will be calculated and provided by the central pathology reader at screening and Visit 9 (or the ET Visit, if applicable), for comparison with screening scores.

8.12.2 Re-Reading of Central Pathologist Assessment of Eligible Patients Based on a Qualifying Historical Biopsy

The site may request a re-read of the central pathologist assessment if the prior results of the patient's historical biopsy met the enrollment criteria. Both fibrosis and NAS criteria must have been met and the report provided to the Sponsor Study Director for approval. Further details of this process are outlined in the Pathology Manual and other related documents.

8.13 Pharmacodynamic Assessments

Evaluation of liver inflammation and fibrosis biomarkers (HOMA-IR, hsCRP, Pro-C3, and ELF panel) will be performed at Visits 2, 5, and 9 (or the ET Visit, if applicable).

8.14 Pharmacokinetic Assessments

For all patients, blood samples for evaluation of trough plasma PK concentrations of NST-4016 will be collected predose at Visits 2 to 9 (or the ET Visit, if applicable).

For those patients participating in the intensive PK subset, PK blood samples will be collected in relation to the first dose of study drug at Visit 2. Samples will be taken at the following timepoints: predose (within 1 hour prior to the first dose), followed by 1, 2, 3, 4, 6, and 8 hours postdose

(±10 minutes) at Visit 2 (Day 0) and 24 hours postdose (±1 hour, but prior to the second dose of study drug on Day 1).

For the intensive PK subset of patients, the following PK parameters will be calculated in order to further characterize the PK of NST-4016 after the first dose:

- AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last observed concentration
- AUC_{0-inf}: area under the plasma concentration-time curve from time 0 extrapolated to infinity
- CL/F: apparent plasma clearance
- C_{max}: maximum observed plasma concentration
- T_{max}: time to reach the maximum observed plasma concentration
- V_z/F: apparent volume of distribution

Additional PK parameters may be determined, if deemed appropriate.

Details of the parameters and handling procedures will be described in the Statistical Analysis Plan.

9 STATISTICS

9.1 Analysis Populations

The Randomized Population will include all patients who are randomized to the study.

The Intent-to-Treat (ITT) Population will include all patients who are randomized and receive at least 1 dose of study drug.

The Modified ITT (mITT) Population will include all patients from the ITT Population who have valid baseline and Week 52 (or ET, if applicable) liver biopsy measurements.

The Per-Protocol (PP) Population will include all patients from the mITT Population who complete the 52-week treatment period without any major protocol violations.

The Trough PK Population will include all patients who received at least 1 dose of NST-4016 and have at least 1 measurable trough PK concentration.

The Intensive PK Population will include all patients who received at least 1 dose of NST-4016 and have at least 1 measurable non-trough intensive PK sample.

The Safety Population will include all patients who receive at least 1 dose of study drug.

9.2 Statistical Methods

Full details of the analyses will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock and unblinding.

9.2.1 Analysis of Efficacy

The efficacy analysis will be performed on the ITT Population; missing values for continuous endpoints will be imputed using multiple imputation methods.

Baseline will be defined as the value at the Screening Visit for measurements from the liver biopsy and imaging data and as the predose value at Visit 2 (Week 0) for the biomarker data. For other efficacy endpoints, baseline will be defined as the predose value at Visit 2 (Week 0); if this value is missing, then the latest predose value will be used.

9.2.1.1 Primary efficacy analysis

The primary endpoint (ie, the percentage of patients with resolution of NASH without worsening fibrosis) will be analyzed using the ITT Population. Patients without a Week 52 (or ET, if applicable) liver biopsy will be imputed as nonresponders. The number and percentage of patients meeting the criteria for the primary endpoint will be summarized by treatment group.

The primary analysis will be conducted using the data from the 600 mg NST-4016 and placebo groups using the Cochran-Mantel-Haenszel test, stratified by biopsy fibrosis score (2 levels: F1 versus F2 or F3). The primary analysis will be based on the use of a 2-sided test at the alpha=0.05 level of significance.

9.2.1.2 Key secondary analysis of the primary endpoint

If the primary analysis is statistically significant ($p<0.05$), the key secondary analysis of the primary endpoint will be conducted using the data from the 300 mg NST-4016 and placebo groups, again using the Cochran-Mantel-Haenszel test, stratified by biopsy fibrosis score

(2 levels: F1 versus F2 or F3). Due to the use of this fixed-sequence testing procedure, the key secondary analysis will be based on the use of a 2-sided test at the alpha=0.05 level of significance. However, if the primary analysis is not statistically significant, the comparison between the 300 mg NST-4016 and placebo groups will be exploratory rather than confirmatory.

9.2.1.3 Sensitivity analysis of the primary endpoint

A sensitivity analysis for the primary endpoint will be carried out using a logistic regression model with treatment group (300 mg NST-4016, 600 mg NST-4016, or placebo) and biopsy fibrosis score (2 levels: F1 versus F2 or F3) as factors. Pairwise treatment comparisons will be estimated in this model as odds ratios (NST-4016 versus placebo) along with their 95% confidence intervals and p-values.

The primary, key secondary, and sensitivity analyses of the primary endpoint will be repeated on the mITT and PP Populations.

9.2.1.4 Secondary efficacy analysis

Continuous efficacy variables will be summarized using descriptive statistics for the observed data and change and/or percent change from baseline by treatment group and visit as appropriate.

Change from baseline to Week 52 in NAS and individual histological scores will be analyzed in an analysis of covariance model, adjusting for treatment (300 mg NST-4016, 600 mg NST-4016, or placebo), biopsy fibrosis score (2 levels: F1 versus F2 or F3), and respective baseline score. Pairwise treatment comparisons between each NST-4016 dose and placebo will be estimated in this model using least square (LS) means, standard errors, 95% confidence intervals, and p-values. A similar analysis will be carried out for the imaging parameters at Week 16 and Week 52.

Efficacy variables measured at multiple timepoints will be analyzed with Mixed Model Repeated Measures methods, with change (or percent change) from baseline as the dependent variable, adjusting for treatment (300 mg NST-4016, 600 mg NST-4016, or placebo), biopsy fibrosis score (2 levels: F1 versus F2 or F3), and baseline score. Pairwise treatment comparisons between each NST-4016 dose and placebo at Week 52 will be estimated using LS means, standard errors, 95% confidence intervals, and p-values.

9.2.1.5 Exploratory biomarker analysis

The analysis of exploratory endpoints will be further described in the Statistical Analysis Plan.

9.2.1.6 Pharmacokinetic analysis

Trough plasma PK concentrations at Visits 3 to 9 will be summarized descriptively by visit for the Trough PK Population.

For the subset of patients with intensive PK sampling data, additional PK parameters will be summarized by treatment using descriptive statistics for the Intensive PK Population. No formal statistical analysis of PK parameters will be performed.

9.2.2 Analysis of Safety

Safety variables will be tabulated and presented for the Safety Population.

Baseline will be defined as the predose value at Visit 2 (Week 0); if this value is missing, then the latest predose value will be used.

A TEAE is defined as a new or worsening adverse event after the first dose of study drug. The number and percentage of patients with at least 1 TEAE will be summarized by treatment group by system organ class and preferred term. Similar summaries will be presented for study drug-related TEAEs and SAEs.

Safety laboratory parameters, vital signs, and ECGs will be summarized by treatment group by visit. Change from baseline values by visit will also be presented for the continuous parameters. The number (and percentage) of patients with abnormalities based on predefined normal ranges will be tabulated by treatment group.

9.2.3 Interim Analysis

An interim analysis was planned for this study after 90 patients had completed 16 weeks of treatment. This analysis was reviewed by the DSMC according to the DSMC Charter. The interim analysis included a comprehensive review of the following data: ALT, AST, HOMA-IR, Pro-C3, ELF panel, MRI-PDFF, cT1, and lipid parameters. The conclusions and recommendations of the DSMC were shared blindly with the Sponsor and clinical sites. A separate interim analysis plan was finalized prior to conducting the interim analysis.

9.2.4 Data Safety Monitoring Committee

An external, independent DSMC will review all available unblinded preliminary safety and biomarker results, as described in the DSMC Charter. The DSMC Charter will describe the overall guidelines, composition and roles, and responsibilities of the independent DSMC for the NST-02 study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study. Patient accrual will continue throughout the period of the DSMC review. The DSMC will advise on the accrual of the remaining patients per protocol or any amendments that are necessary for safety reasons.

9.2.5 Sample Size Determination

A sample size of 88 patients per treatment group provides 80% power to detect a 40% responder rate for active versus placebo, assuming a placebo response rate of 18% and a dropout rate of 25%.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events
- WHO Drug Dictionary for prior and concomitant medications

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation, and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs

and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the Food and Drug Administration, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13 REFERENCES

1. NorthSea Therapeutics BV. Investigator's Brochure NST-4016 (Icosabutate). Version 7, 24 January 2018.
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APPENDIX A: SCHEDULE OF PROCEDURES

	Screening[a]	Treatment Period								Safety Follow-up[b]	ET Visit[b]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	
Study Week	**-8 to -1**	**0**	**4**	**10**	**16**	**24**	**32**	**40**	**52**	**54**	
Study Day	**-56 to -1**	**0**	**28**	**70**	**112**	**168**	**224**	**280**	**364**	**378**	
Visit Window		**±0 days**	**±5 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±5 days**	
Assessment											
Informed consent	X										
Eligibility criteria	X	X[c]									
Demographics	X										
Medical history	X	X									
Prior/concomitant medications[d]	X	X	X	X	X	X	X	X	X	X	X
Height and body weight[e]	X	X	X	X	X	X	X	X	X	X	X
BMI calculation	X	X									
Physical examination[f]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X
AUDIT-C[h]	X										
Viral serology[i]	X										
Fasting hematology, biochemistry, coagulation, and lipid panels[j]	X	X	X	X	X	X	X	X	X	X	X
Lipoprotein particle size		X			X				X		X
Urinalysis[k]	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[l]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[m]	X	X			X		X		X	X	X
FibroScan®	X[n]										
MRI-PDFF and cT1 imaging[o]	X	X[p]			X				X		X
Liver biopsy	X[q]								X[r,s]		X[b]
Randomization		X									
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X
Biomarker sampling[t]		X			X				X		X
PK sampling[u]		X[v]	X	X	X	X	X	X	X		X

Lipidomic analyses sampling[w]		X							X		X
Study drug administration/ dispensing[r,x]		X	X	X	X	X	X	X			
Study drug accountability[y]			X	X	X	X	X	X	X		X

COVID-19 contingency measures: This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to visit schedules and procedures specific to situations where COVID-19 is impacting study conduct. See Appendix G for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

a. The screening period of up to 8 weeks may include more than 1 visit. Patients who screen fail may be rescreened once.
b. Patients who discontinue early from the study for any reason prior to completion of the treatment period will be requested to return to the clinic for an ET Visit as soon as possible after their last intake of study drug. Liver biopsy at ET will be only performed for patients who have been on study drug for at least 6 months. If a patient discontinues early from the study for any reason after completion of the treatment period but before the Safety Follow-up Visit, sites should make every attempt to bring the patient into the site for the Safety Follow-up Visit.
c. Eligibility criteria will be reassessed prior to dosing with study drug to ensure no changes in eligibility have occurred since screening.
d. All prior and concomitant medications will be documented in the eCRF. Prior medications include any medication taken within 6 months prior to screening. Concomitant medications include any medication taken on or after the date the patient signs informed consent. Unless medically warranted, all concomitant medications should remain stable from screening through the Safety Follow-up Visit (Visit 10). Throughout the duration of the study, patients should not introduce changes to their usual diet (including dietary supplements) or lifestyle. Any changes to concomitant medication dosing during the study will be captured in the eCRF and closely monitored.
e. Height will be measured at screening only. Body weight will be measured at every visit.
f. Full physical examinations (including general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological systems; mental status; and extremities) will be performed at screening; Visits 2 and 9; and at study exit (whether at the Safety Follow-up or ET Visit). Abbreviated physical examinations will be performed at all other visits.
g. Vital signs will include blood pressure, pulse rate, and body temperature, and will be performed with the patient in the sitting position after 5 minutes of rest and before any blood draws. Three replicate blood pressure readings will be taken at each visit.
h. Only patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT at screening and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
i. Patients must test negative for hepatitis B virus, HCV (patients with a confirmed history of HCV infection can be included if HCV PCR is negative for at least the last 2 years), and HIV infection to be eligible for the study.
j. If a patient has a qualifying historical biopsy, the required AST levels (AST ≥20 U/L in men and ≥17 U/L in women by central laboratory or AST ≥30 U/L by a local laboratory within 60 days of screening) will not apply.
k. Further analysis of urine sediment or urine microscopy will be performed if there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite.
l. For women of childbearing potential, a serum hCG pregnancy test will be performed at screening, Week 0, and at study exit (whether at the Safety Follow-up or ET Visit). Urine hCG testing will be performed at all other visits. If a urine hCG test is positive, pregnancy will be confirmed by a serum hCG test. Follicle-stimulating hormone level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.
m. Single 12-lead ECGs will be performed after the patient has been resting in the supine position for at least 10 minutes. In case of evident bad quality of the tracing (eg, muscle tremor), the ECG will be repeated. QTcF will be measured.
n. Patients without a historical biopsy must have a FibroScan® VCTE measurement ≥8.5 kPa and a CAP for steatosis with cut-off values ≥300 dB/m at screening or a historical FibroScan (with eligible VCTE and CAP values) within 90 days of screening. FibroScan is not required for patients who have evaluable histology slides from a liver biopsy performed in the previous 6 months available for review by the central pathology reader.
o. At screening, perform MRI-PDFF if FibroScan values (VCTE and CAP) are within eligibility range (for patients without historical biopsy) or if the patient has a qualifying historical biopsy. If the patient is eligible based on a historical biopsy, the MRI-PDFF procedure should be performed but the eligibility criterion of liver fat content ≥8% will not be applied. Magnetic resonance imaging-PDFF will be performed using a standardized central imaging protocol and will be validated by the central imaging reader at screening (as the baseline value), Visit 5 (Week 16), and Visit 9 (Week 52) or the ET Visit. Iron-corrected T1 will be calculated for all randomized patients at Visit 2 (Week 0) (using the screening MRI), Visit 5 (Week 16), and Visit 9 (Week 52) or the ET Visit.

p. At Visit 2, cT1 will be calculated from the screening MRI only if the patient is randomized. No MRI will be performed at Visit 2.
q. Historical liver biopsy within 6 months of screening may be used for eligibility if evaluable histology slides are available for review by the central pathology reader. Patients must not have received nonalcoholic steatohepatitis therapy since the historical biopsy was obtained. Historical liver biopsies obtained during the course of a prior investigational drug study must not be utilized if obtained within 3 months or 5 half-lives of the last dose of the prior investigational drug, whichever is longer.
r. In the event that the Visit 9 biopsy is delayed, patients will continue to administer study drug daily until the biopsy occurs for up to 30 days after the originally projected Visit 9 date.
s. In a subgroup of patients, biopsy tissue collected at the End of Treatment/Visit 9 will be used to perform lipidomic analyses.
t. Biomarkers to be assessed include: HOMA-IR, hsCRP, Pro-C3, and ELF panel.
u. Pharmacokinetic sampling will occur at Visits 2 to 9 at time 0 (predose, ie, within 1 hour prior to the first dose).
v. For those patients participating in the intensive PK subset, PK blood samples will be collected in relation to the first dose of study drug at Visit 2. Samples will be taken at the following timepoints: predose (within 1 hour prior to the first dose), followed by 1, 2, 3, 4, 6, and 8 hours postdose (±10 minutes) at Visit 2 (Day 0) and 24 hours postdose (±1 hour, but prior to the second dose of study drug on Day 1).
w. In a subgroup of patients, fasting serum samples will be collected to perform lipidomic analyses.
x. On Visits 2 to 8, study drug will be administered to the patient on site to accommodate trough PK sampling prior to dosing. Sufficient study drug will be dispensed to the patient for dosing until the next study visit.
y. Returned and used/unused study drug will be collected to assess compliance.

AUDIT = Alcohol Use Disorders Identification Test; AUDIT-C = Alcohol Use Disorders Identification Test-Concise; BMI = body mass index; CAP = controlled attenuation parameter; COVID-19 = Coronavirus Disease 2019; cT1 = iron-corrected T1; ECG = electrocardiogram; eCRF = electronic case report form; ELF = enhanced liver fibrosis; ET = Early Termination; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; hsCRP = high-sensitivity C-reactive protein; MRI-PDFF = magnetic resonance imaging-proton density-fat fraction; PCR = polymerase chain reaction; PK = pharmacokinetics; VCTE = vibration-controlled transient elastography.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Biochemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate
Gamma glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin [1]
Total protein	Uric acid

1. If total bilirubin is above the upper limit of normal, add conjugated (direct) bilirubin.

Hematology

Hematocrit	Hemoglobin
Neutrophils	Platelets
Red blood cell count	White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Lipid and Metabolic Profile

Apolipoprotein B	Apolipoprotein C3
Hemoglobin A1c	High-density lipoprotein-cholesterol
Lipoprotein(a)	Lipoprotein particle size [1]
Low-density lipoprotein-cholesterol	Remnant cholesterol
Serum cholesterol	Triglycerides

1. Lipoprotein particle size will be assessed only at baseline, Week 16, and at the end of treatment (Week 52/Early Termination).

Plasma/Serum and Liver Lipidomics

Acyl carnitines	Acyl-ether-phospholipids
Amino acids	Bile acids
Cholesteryl esters	Diacyl-phospholipids
Fatty acids	Glycerolipids
Icosabutate and icosabutate metabolites	Lyso-phospholipids
N-acyl ethanolamines	Oxidized fatty acids
Primary fatty acid amides	Sphingolipids

Coagulation

Activated partial thromboplastin time	Fibrinogen
International normalized ratio	Prothrombin time

Liver Inflammation and Fibrosis Biomarkers

Enhanced liver fibrosis panel	High-sensitivity C-reactive protein
Homeostatic Model Assessment for Insulin Resistance	Pro-C3

Endocrinology

Human chorionic gonadotropin (hCG) [1]	Follicle-stimulating hormone (FSH) [2]
Thyroid-stimulating hormone (TSH) [3]	

1. For women of childbearing potential, a serum hCG pregnancy test will be performed at screening, Week 0, and at study exit (whether at the Safety Follow-up Visit or Early Termination Visit). Urine hCG testing will be performed at all other visits. If a urine hCG test is positive, pregnancy will be confirmed by a serum hCG test.
2. FSH level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.
3. Free triiodothyronine and free thyroxine will be measured if TSH is abnormal.

Urinalysis [1]

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Dipstick urine qualitatively. Further analysis of urine sediment or urine microscopy will be performed if there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite.

Serology

Hepatitis B surface antigen	Hepatitis C virus antibody (and polymerase chain reaction ribonucleic acid for positive antibody samples)
Human immunodeficiency virus	

APPENDIX C: ALCOHOL USE DISORDERS IDENTIFICATION TEST-CONCISE

The Alcohol Use Disorders Identification Test-Concise (AUDIT-C) has 3 questions and is scored on a scale of 0 to 12. Read the questions as written and circle the letter that corresponds to the answer. Each AUDIT-C question has 5 answer choices valued from 0 to 4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive. Generally, the higher the score, the more likely it is that a person's drinking is affecting his or her safety.

AUDIT-C Questionnaire

Patient ID _____ Visit date _____

1. **How often do you have a drink containing alcohol?**
   a. Never
   b. Monthly or less
   c. 2-4 times a month
   d. 2-3 times a week
   e. 4 or more times a week

2. **How many standard drinks containing alcohol do you have on a typical day?**
   a. 1 or 2
   b. 3 or 4
   c. 5 or 6
   d. 7 to 9
   e. 10 or more

3. **How often do you have six or more drinks on one occasion?**
   a. Never
   b. Less than monthly
   c. Monthly
   d. Weekly
   e. Daily or almost daily

See answer module on the next page.

Answer Module

Question 1: How often do you have a drink containing alcohol?

Valid Values

Value	Value Meaning	Description	Display Order
Never	Never	Not ever; at no time in the past (or future).	0
Monthly or less	Monthly or less	Monthly or less	1
2 to 4 times a month	Two To Four Instance Per Month	A natural number greater than 1 and less than 3 and the quantity that it denotes: the sum of one and one.: Used as a function word to indicate direction, purpose, or movement.: A natural number greater than 3 and less than 5 and the quantity that it denotes: the sum of three and one.: An occurrence of something.: For each, generally denoting a ratio.: One of the 12 divisions of a year as determined by a calendar. It corresponds to the unit of time of approximately to one cycle of the moon's phases, about 30 days or 4 weeks.	2
2 to 3 times a week	Two To Three Instance Per Week	A natural number greater than 1 and less than 3 and the quantity that it denotes: the sum of one and one.: Used as a function word to indicate direction, purpose, or movement.: A natural number greater than 2 and less than 4 and the quantity that it denotes: the sum of two and one.: An occurrence of something.: For each, generally denoting a ratio.: Any period of seven consecutive days.	3
4 or more times a week	Four Or Greater Than Integer::4 Instance Per Week	A natural number greater than 3 and less than 5 and the quantity that it denotes: the sum of three and one.: An article used to connect words, phrases, or clauses representing alternatives; used to connect alternative terms for the same thing; used in correlation; used to correct or rephrase what was previously said; otherwise.: A statement about the relative size or order of two objects specifying that an object of interest exceeds another object in quantity or measure or value or status.: A number with no fractional part.::4: An occurrence of something.: For each, generally denoting a ratio.: Any period of seven consecutive days.	4

Question 2: How many standard drinks containing alcohol do you have on a typical day?

Valid Values

Value	Value Meaning	Description	Display Order
1 or 2	1 or 2	1 or 2	0
3 to 4	3 to 4	3 to 4	1
5 to 6	5 to 6	5 to 6	2
7 to 9	7 to 9	7 to 9	3
10 or more	10 or more	10 or more	4

Question 3: How often do you have six or more drinks on one occasion?

Valid Values

Value	Value Meaning	Description	Display Order
Never	Never	Not ever; at no time in the past (or future).	0
Less than monthly	Less Than Monthly	A statement about the relative size or order of two objects specifying that an object of interest is smaller than another object in quantity or measure or value or status.: Every month.	1
Monthly	Monthly	Every month.	2
Weekly	Weekly	Every week.	3
Daily or almost daily	Daily	Occurring or done each day.	4

APPENDIX D: ALCOHOL USE DISORDERS IDENTIFICATION TEST: INTERVIEW VERSION

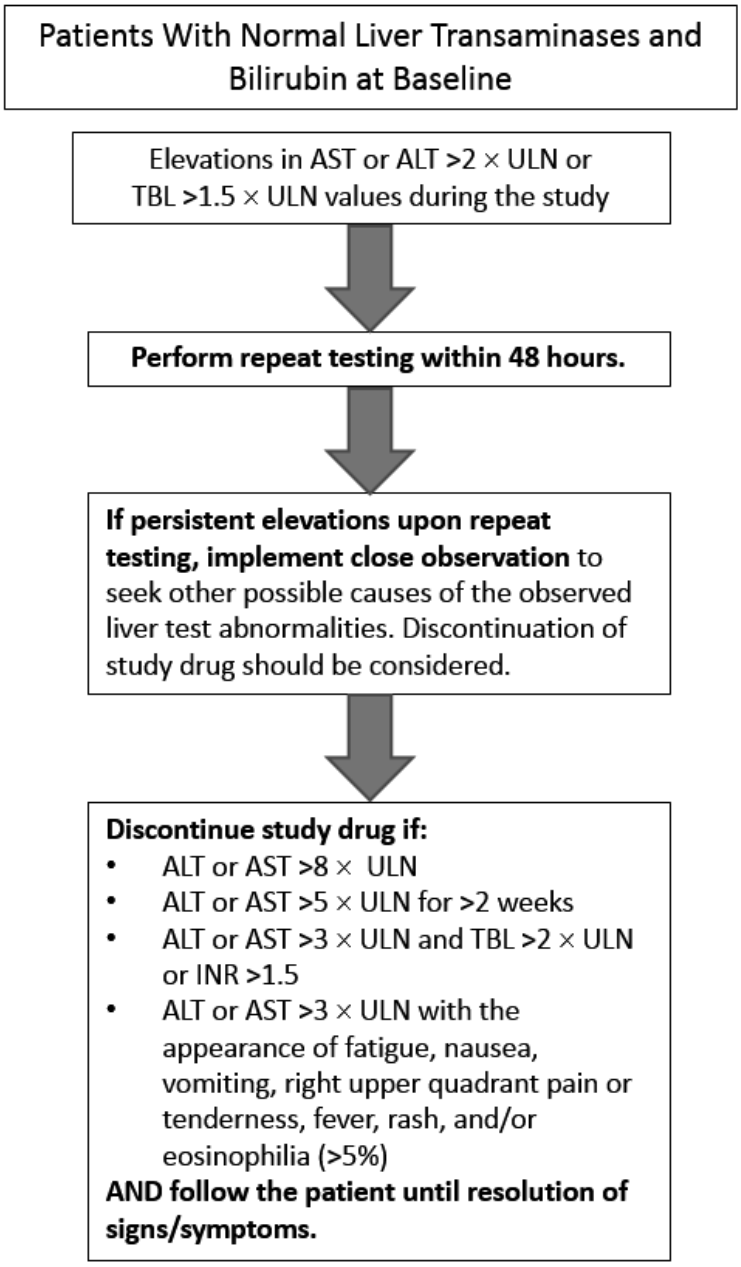
Read questions as written. Read answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks." Place the correct answer number in the box at the right. Total scores of ≥8 are recommended as indicators of hazardous and harmful alcohol use.

1. How often do you have a drink containing alcohol? (0) Never [Skip to Qs 9-10] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week ☐	6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
2. How many drinks containing alcohol do you have on a typical day when you are drinking? (0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more ☐	7. How often during the last year have you had a feeling of guilt or remorse after drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily *Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0* ☐	8. How often during the last year have you been unable to remember what happened the night before because you had been drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
4. How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	9. Have you or someone else been injured as a result of your drinking? (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
5. How often during the last year have you failed to do what was normally expected from you because of drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down? (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
Record total of specific items here ☐ *If total is greater than recommended cut-off, consult User's Manual.*	

APPENDIX E: DRUG-INDUCED LIVER INJURY MONITORING PLAN

Throughout the study, all treatment-emergent adverse events, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for suspected drug-induced liver injury as detailed in this Monitoring Plan.

Patients with normal liver transaminases and bilirubin at baseline



ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

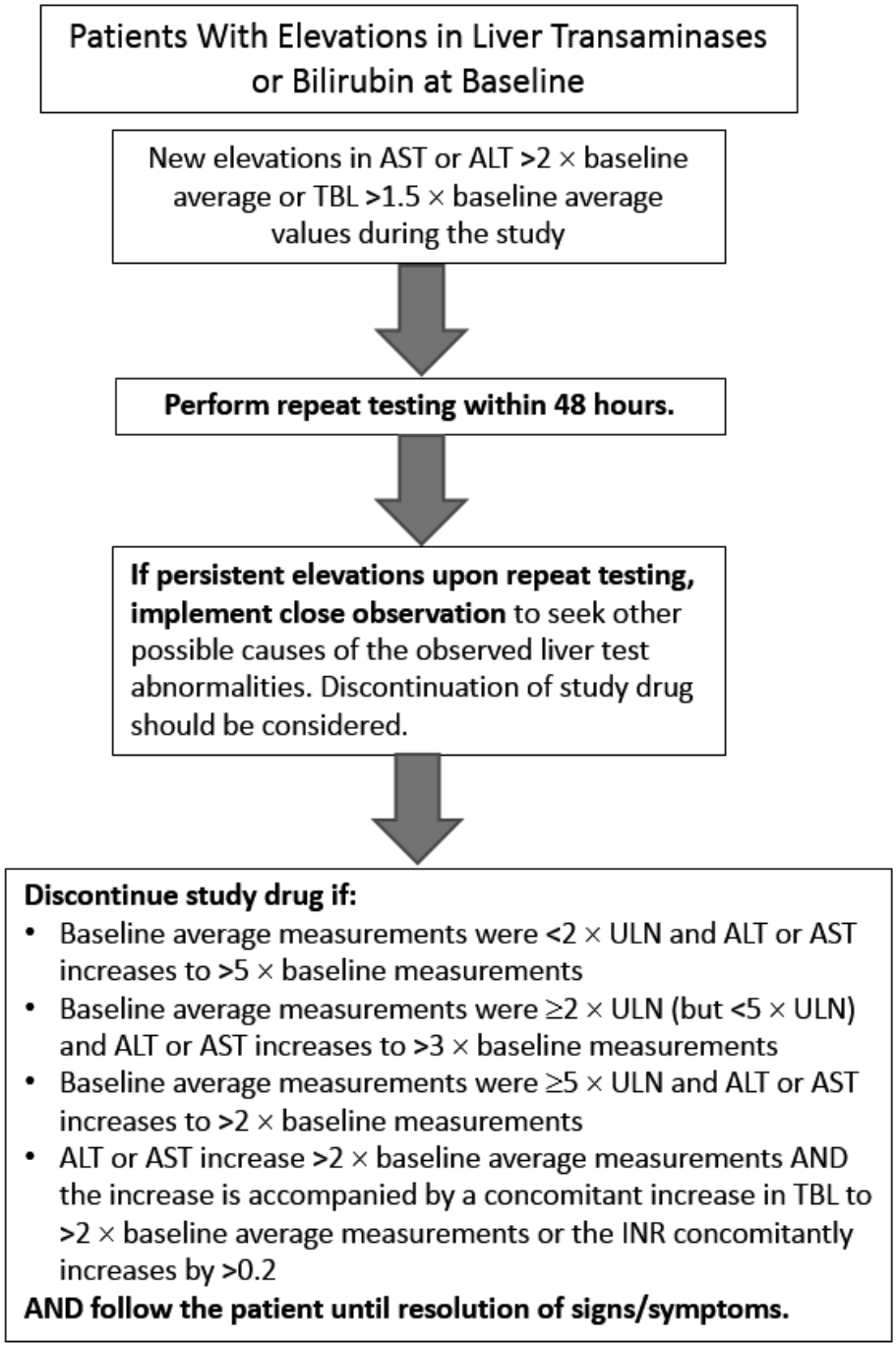
Suspected drug-induced liver injury monitoring in patients with normal liver transaminases and bilirubin at baseline should be performed throughout the study according to the procedures summarized below.

- If patients with normal baseline liver indices develop elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × upper limit of normal (ULN) or total bilirubin (TBL) >1.5 × ULN values during the study, repeat testing should be performed within 48 hours.
    - If there are persistent elevations (ALT or AST >2 × ULN or TBL >1.5 × ULN) upon repeat testing, close observation (testing and physical examination 2 to 3 times per week) should be implemented. An important purpose of the close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following: acute viral hepatitis, alcoholic and autoimmune hepatitis, hepatobiliary disorders, cardiovascular causes, or concomitant treatments. Discontinuation of study drug should be considered.
- Study drug should be discontinued, and the patient should be followed until resolution of signs or symptoms, in the following situations:
    - ALT or AST >8 × ULN.
    - ALT or AST >5 × ULN for more than 2 weeks.
    - ALT or AST >3 × ULN and (TBL >2 × ULN or international normalized ratio [INR] >1.5).
    - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (ie, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]), perform liver function tests to determine if liver disease is worsening and discontinue the study drug if worsening is confirmed.

Reinitiation of study drug may be considered after consultation with the Medical Monitor.

Patients with elevations in liver transaminases or bilirubin at baseline



ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Suspected drug-induced liver injury monitoring in patients with elevations in liver transaminases or bilirubin at baseline should be performed throughout the study according to the procedures summarized below.

- If patients with abnormal baseline liver indices develop elevations of AST or ALT >2 × baseline average or TBL >1.5 × baseline average values during the study, repeat testing should be performed within 48 hours.
    - If there are persistent elevations (ALT or AST >2 × baseline average or TBL >1.5 × baseline average values) upon repeat testing, then close observation (testing and physical examination 2 to 3 times per week) should be implemented and discontinuation of study drug should be considered.
- Discontinue the study drug if any of the following occur:
    - Baseline average measurements were <2 × ULN and ALT or AST increases to >5 × baseline measurements.
    - Baseline average measurements were ≥2 × ULN (but <5 × ULN as per eligibility requirements) and ALT or AST increases to >3 × baseline measurements.
    - Baseline average measurements were ≥5 × ULN and ALT or AST increases to >2 × baseline measurements.
    - ALT or AST increase >2 × baseline average measurements AND the increase is accompanied by a concomitant increase in TBL to >2 × baseline average measurements or the INR concomitantly increases by >0.2.

For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (ie, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]), perform liver function tests to determine if liver disease is worsening and discontinue the study drug if worsening is confirmed.

Reinitiation of study drug may be considered after consultation with the Medical Monitor.

<u>For all patients, close observation for suspected drug-induced liver injury includes the following:</u>

- Repeating liver enzyme (ALT, AST, and alkaline phosphatase) and serum bilirubin tests 2 or 3 times weekly (if a patient lives in a remote area, he or she can be tested locally and the results promptly communicated to the study site).
- The frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
- 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.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

APPENDIX F: 2018 AMERICAN HEART ASSOCIATION/AMERICAN COLLEGE OF CARDIOLOGY GUIDELINE ON THE MANAGEMENT OF BLOOD CHOLESTEROL

The manuscript (to appear in the Journal of the American College of Cardiology [ACC]) of the 2018 American Heart Association (AHA)/ACC Guideline on the Management of Blood Cholesterol[1] can be accessed at the following link:

https://www.ahajournals.org/doi/10.1161/cir.0000000000000625

The "Guidelines Made Simple" version of the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol, which contains excerpts from the full guideline, can be accessed at the following link:

https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Guidelines/2018/old_Guidelines-Made-Simple-Tool-2018-Cholesterol.pdf

[1] Grundy SM, Stone NJ, Bailey AL, et al.
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll of Cardiol*. 2018. Nov 8. pii: S0735-1097(18)39034-X. doi: 10.1016/j.jacc.2018.11.003. [Epub ahead of print].

APPENDIX G: CORONAVIRUS DISEASE 2019 CONTINGENCY MEASURES

The following contingency measures have been established to mitigate the potential impact that Coronavirus Disease 2019 (COVID-19) has on study conduct, patient safety, and data integrity. It is important to note that these mitigations are specific to situations where COVID-19 is impacting study conduct. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

Visit schedule and procedures

- Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 10 windows extended to ±14 days as long as study drug supply is sufficient. If the extended window is used, any accompanying study drug interruption should not exceed 14 days.
- The screening period may be extended to a total of 12 weeks to account for potential delays in scheduling screening assessments. If the extended screening window is used, Investigators must ensure that the screening magnetic resonance imaging-proton density-fat fraction assessment is conducted within 8 weeks of randomization.
- If on-site visits cannot occur, assessments and safety follow-up may occur via telehealth, local community laboratories, and in-home visits by qualified nurses. The following visits may be replaced by telehealth or in-home visits: Visit 3, Visit 4, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 10.
- Every effort should be made to utilize the central laboratory for study-specific laboratory assessments. If the patient must report to a local community laboratory for safety follow-up purposes, the following samples should be ordered from the local laboratory: biochemistry panel, hematology panel, coagulation, hemoglobin A1c, and low-density lipoprotein-cholesterol. Refer to Appendix B of the protocol to ensure all required analytes in a given laboratory panel are being collected by the local laboratory.

Study drug dispensation

- Patients may be supplied with additional study drug during a visit if there is a concern that the patient may not be able to report to the site as scheduled for the next required visit. This will ensure that patients have enough study drug to accommodate extended visit windows or telehealth visits.
- In some circumstances, it may be necessary to ship study drug directly to the patient. Shipping will be performed by a qualified professional courier who is contracted by the Sponsor or Contract Research Organization. The courier will be responsible for providing packing materials and cold chain monitoring to complete the shipment. Patients must consent to providing personal data to the courier to complete the shipment. Refer to the Pharmacy Manual for additional details.