BEMPEDOIC ACID

1002-046

A RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BEMPEDOIC ACID (ETC-1002) 180 MG COMPARED TO PLACEBO ADDED TO BACKGROUND LIPID-MODIFYING THERAPY IN PATIENTS WITH ELEVATED LDL-C WHO ARE STATIN INTOLERANT

Study Phase:	3
IND Number:	106654
EudraCT Number:	NA
Indication:	Treatment of hyperlipidemia
Investigators:	Approximately 71 sites located in North America
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108 Phone: 734-862-4840 Fax: 734-582-9720
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

Version	Date
Original Protocol:	25 August 2016
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Confidentiality Statement

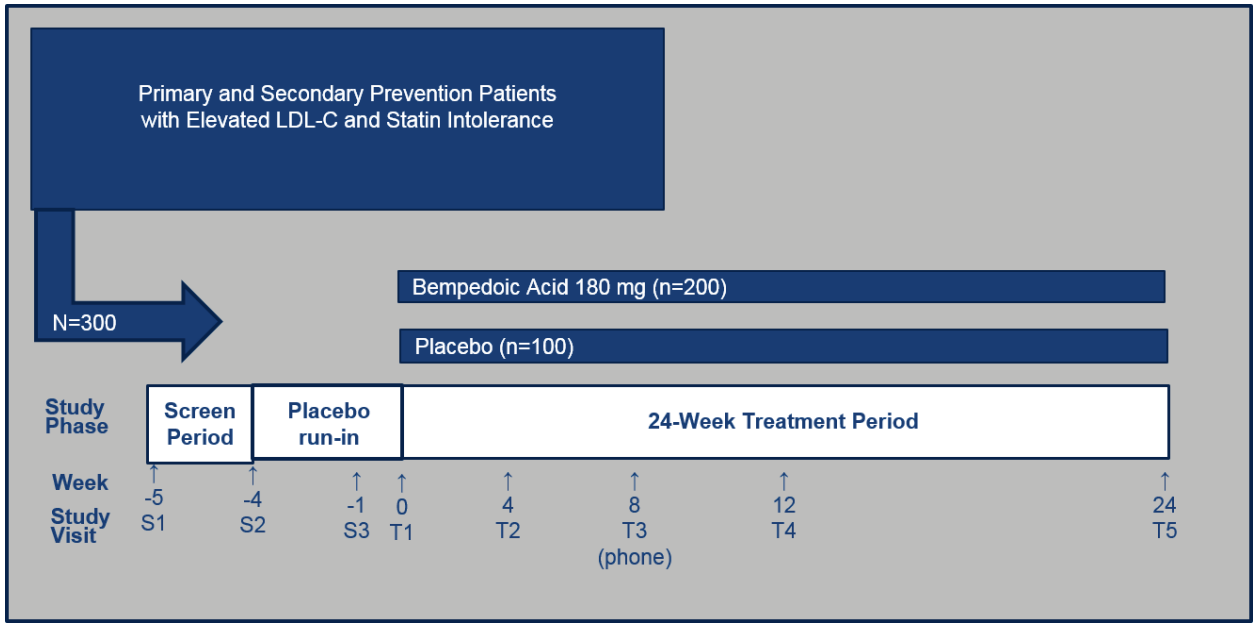
NCT number: NCT02988115
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.
Name of Investigational Product: Bempedoic acid (ETC-1002) film-coated tablets
Name of Active Ingredient: Bempedoic acid
Title of Study: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant
Study Number: 1002-046
Phase of Development: 3
Clinical Sites: Approximately 71 sites located in North America
Objectives: **Primary:** • To assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing low-density lipoprotein cholesterol (LDL-C) in statin intolerant patients with elevated LDL-C **Secondary:** • To evaluate the effect of 24-week treatment with bempedoic acid 180 mg/day versus placebo on LDL-C • To evaluate the effect of bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-sensitivity C-reactive protein (hs-CRP), and apolipoprotein B (apoB) after 12 weeks of treatment • To evaluate the 24-week safety and tolerability of bempedoic acid 180 mg/day compared to placebo **Tertiary:** [redacted]

Methodology:

1002-046 Study Design



This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 71 clinical sites in North America. Screening Week -5 (Visit S1) will be approximately 5 weeks prior to randomization. The time period between Visits S1 and S2 can be extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons as specified in the protocol. Eligible patients will return to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo study drug. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel regarding their eligibility status and considered screen failures. As necessary, for reasons of safety if a patient begins the run-in period but screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of adverse events (AEs).

Approximately 300 patients with a history of statin intolerance (SI) (defined as an inability to tolerate 2 or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued) will be stratified based on patient type (primary prevention; secondary prevention) and randomized at Week 0 (Visit T1) in a 2:1 ratio to receive either bempedoic acid 180 mg (n = 200) or matching placebo (n = 100) once daily for 24 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), and Week 24 (Visit T5). A phone visit will occur at Week 8 (Visit T3). An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety data from this and other ongoing Phase 3 studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: cardiovascular (CV) death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction [MI] (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.

Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C

Secondary Endpoints

1. Percent change from baseline to Week 24 in LDL-C
2. Percent change from baseline to Week 12 in non-HDL-C, TC, apoB, and hs-CRP
3. Absolute change from baseline to Weeks 12 and 24 in LDL-C

Tertiary Endpoints

[redacted]

Safety Endpoints

1. Patient incidence of treatment-emergent adverse event (TEAE)
2. Safety laboratory values and vital signs
3. Cardiovascular event rates

Number of patients (planned): Approximately 300 adult male and female patients

Diagnosis and Criteria for Inclusion:

Key inclusion criteria

1. Provision of written informed consent must be obtained prior to any study-specific procedure.
2. Men and nonpregnant, nonlactating women. Women must be either:
   - Naturally postmenopausal defined as ≥1 year without menses and:
     - ≥55 years, **or**
     - <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   - Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; **or**
   - Women of childbearing potential must be willing to use 2 acceptable methods of birth control (unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:
     - oral, implanted, topical, or injectable birth control medications
     - placement of an intrauterine device with or without hormones
     - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
     - vasectomized male partner who is the sole partner for this patient
     - true abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

   There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
3. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -5 (Visit S1)
4. Fasting (minimum of 10 hours) calculated LDL-C at Week -5 (Visit S1)

- Primary prevention ≥130 mg/dL (3.4 mmol/L)
- Secondary prevention and/or heterozygous familial hypercholesterolemia (HeFH) ≥100 mg/dL (2.6 mmol/L)
- All patients must have fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3)

In the case of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor use, the patient must have received 3 stable doses. It is important that lipid values are measured at PCSK9i trough levels. Therefore, study visits should be scheduled in accordance with the patient's PCSK9i injection regimen so that measurement of lipid values for all visits occurs before the PCSK9i injection but not greater than 48 hours before the next scheduled PCSK9i injection. Patients who have discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least 4 months prior to Screening Visit S1.

5. Requiring lipid-modifying therapy for the purpose of primary or secondary prevention of cardiovascular events.
   - Primary Prevention patients must as a minimum have a history of requiring lipid-modifying therapy based on local guidelines (for example, American College of Cardiology [ACC]/American Heart Association [AHA] guidelines, European Society of Cardiology [ESC]/European Atherosclerosis Society [EAS] guidelines, Canadian Cardiovascular Society guidelines).
   - Secondary prevention and/or HeFH patients must include those with a history of:
     - HeFH, defined by:
     - Genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 5) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 6).

       and/or
     - Coronary artery disease, defined by:
       - MI (either ST-elevation MI or non-ST-elevation MI) occurring greater than 90 days prior to screening (Week -5 Visit S1), **or**
       - Percutaneous coronary or surgical coronary revascularization, occurring greater than 90 days prior to screening (Week -5 Visit S1), **or**
       - Angiographic stenosis of >50% in a least 1 major coronary artery (native or graft vessel), as documented by selective coronary angiography or computed tomography angiography (CTA), **or**
     - Symptomatic peripheral arterial disease (PAD), defined by:
       - Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index ≤0.9 performed by a vascular lab or angiogram (including CTA) showing ≥50% stenosis, **or**
       - Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening (Week -5, Visit S1), **or**
       - Abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring greater than 90 days prior to screening (Week -5, Visit S1), **or**
       - Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening (Week -5, Visit S1), **or**
     - Cerebrovascular atherosclerotic disease defined by:
       - Ischemic stroke occurring greater than 90 days prior to screening (Week -5 Visit S1), **or**

- Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram, occurring greater than 90 days prior to screening (Week -5 Visit S1).

6. Patient reported SI defined as an inability to tolerate 2 or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued.

   Low-dose statin therapy is defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg.

   Please note that patients currently tolerating very-low-dose statin therapy (an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg) are considered to be intolerant to that low-dose statin. Patients may continue taking very-low-dose statin therapy throughout the study provided that it is stable (used for at least 4 weeks prior to Screening Visit S1) and well tolerated.
7. Written confirmation by both patient and principal investigator that the patient is statin intolerant as defined above and aware of the benefit of statin use to reduce the risk of MACE including cardiovascular death.

Key exclusion criteria

1. Total fasting (minimum of 10 hours) TG ≥500 mg/dL (5.6 mmol/L at Week -5 (Visit S1).

   Note: A single repeat, fasting (minimum of 10 hours) of TG may be completed prior to initiation of the single-blind Run-in period. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.
2. Renal dysfunction or a glomerulonephropathy, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Week -5 (Visit S1).

   Note: A single repeat of eGFR may be completed between Visits S1 and S2. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.
3. Body mass index (BMI) ≥50 kg/m^2
4. Recent (within 3 months prior to the screening visit [Week -5 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.
5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg measured according to local standards.

   Note: At the discretion of the investigator, the time between Visits S1 and S2 can be extended by 4 weeks for adjustments in blood pressure (BP) medications and/or additional assessment of BP, with the repeat assessment value used to determine eligibility. Alternatively, patients can be rescreened if BP status has changed.
6. Hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -5 (Visit S1).
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.

8. Liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -5 (Visit S1).
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥1.2 × ULN at Week -5 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

   Note: At the discretion of the investigator, a single repeat of ALT, AST, and/or TB may be completed prior to randomization. For those patients who have a repeat ALT and/or AST, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption.
10. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Week -5 (Visit S1).
11. Persistent poor compliance or lack of tolerance with single-blind, placebo study drug (ie, ingesting <80% average of planned doses) assessed at the T1 visit prior to randomization.
12. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.
13. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
14. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other meds for chronic pain that have been stable, without evidence of abuse, and prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
15. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood transfusion, or major surgery with or without blood loss within 30 days prior to randomization.
16. Use of any experimental or investigational drugs within 30 days.
17. Previous enrollment in an Esperion bempedoic acid clinical study.
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Week -5 [Visit S1]),
    - Lomitapide or apheresis therapy (must be stopped at least 3 months prior to Week -5 [Visit S1]),
    - Red yeast rice extract and berberine-containing products must be stopped at least 2 weeks prior to Week -5 [Visit S1]),
    - Use of an investigational cholesterol ester transfer protein (CETP-I) within the last 2 years (except evacetrapib within the last 3 months).
    - Statins are prohibited at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg.

      Note: Patients can be on any available lipid-modifying therapy with the exception of the exclusions listed above as long as they have been stable on oral medications for 4 weeks prior to Screening Visit S1 and are taken at a consistent time each day.
19. Planned initiation or changes to the following drugs:

- Hormone replacement (6 weeks prior to randomization)
- Thyroid replacement (6 weeks prior to randomization)
- Diabetes medications (4 weeks prior to randomization)
- Obesity medication (4 weeks prior to randomization)
- PCSK9 inhibitors: Patients who are currently on a stable, commercially available PCSK9 inhibitor (alirocumab or evolocumab) must have had at least 3 doses prior to Visit S1. Patients who were previously (either investigational or commercial) on a PCSK9 inhibitor, must wait at least 4 months after last dose prior to screening (Week -5, Visit S1).

20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
22. Pregnant, breastfeeding, or intending to become pregnant within 30 days after last dose of study drug.
23. Patients who have enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9.
24. In patients taking very low dose statins, gemfibrozil is excluded per the co-administration prescribing instructions.

Test product, dose, and mode of administration:

- Bempedoic acid 180-mg tablets
- Matching placebo tablets

All study drug (bempedoic acid or placebo) will be ingested once daily with or without food

Duration of treatment:

The duration of treatment will be a 5-week screening period followed by a 24-week treatment period.

Criteria for evaluation:

Efficacy:

Lipid and Cardiometabolic Assessments:

- Calculated LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP
  - If TG exceeds 400 mg/dL (4.5 mmol/L) or LDL-C is ≤50 mg/dL (1.3 mmol/L), direct measure of LDL-C will be conducted.

Safety:

Safety Assessments:

Adverse events and SAEs will be collected and reported. Clinical endpoints will be collected and adjudicated by an independent CEC. Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, coagulation, HbA_{1C}, fasting glucose, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram (ECG) readings, and weight.

Clinical Laboratory Assessments:

- Hematology: Hematocrit (Hct), Hgb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute values only)
- Urinalysis (Dipstick): Clarity, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen
- Urinalysis (Microscopic): Obtain centrally only if positive urine dipstick; bacteria, casts, crystals, epithelial cells, RBC, and WBC
- Coagulation: Prothrombin time (PT) and International Normalized Ratio (INR)

  In patients receiving anticoagulant therapy PT/INR must be evaluated at Visit T1 and 3 to 5 days post Visit T1 using local or central lab
- Serum Chemistry (fasting): Albumin (ALB), alkaline phosphatase (ALK-P), ALT (or serum glutamic pyruvic transaminase [SGPT]), AST (or serum glutamic oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO_2), chloride (Cl), creatinine, CK, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid
- HbA_{1C}

Other Screening Laboratories:

- Serum pregnancy test (only for females who are of childbearing potential) with urine pregnancy test at T1, FSH (naturally postmenopausal females <55 years of age at screening and >1 year without menses)
- HBsAg, hepatitis C virus (HCV)
- TSH

Other Assessments:

- Trough plasma concentrations of bempedoic acid and its metabolite ESP15228 will be collected before dose at Weeks 4, 12, and 24

Safety and Monitoring:

Monitoring and Management Plans for Triglyceride Elevations:

Elevated Triglycerides:

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds 1000 mg/dL (11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >1000 mg/dL (11.3 mmol/L) will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value

meets the threshold criteria

- Any patient with a confirmed TG >1000 mg/dL (11.3 mmol/L) may initiate standard-of-care therapy (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.
- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from investigational medicinal product (IMP) treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

Monitoring and Management of Potential AEs and Adverse Events of Special Interest (AESI)

Potential AEs:

Based on findings in nonclinical models, potential AEs include reversible hypoglycemia and metabolic acidosis. Potential cases of reversible hypoglycemia and metabolic acidosis will be identified by routine safety monitoring of AEs and clinical safety laboratories.

Musculoskeletal Safety:

Patients with CK abnormalities will also be reviewed for any other lab changes, such as creatinine, and any reported AEs or SAEs. Musculoskeletal events will be identified and evaluated by routine safety monitoring of PE findings and AEs.

Hepatic:

Hepatic function will be monitored throughout with the clinical safety labs. More detailed investigation will occur per the instructions in the protocol body if the safety clinical laboratory results are 3 times or more than the ULN.

Renal:

Renal function will be monitored throughout with clinical safety labs. More detailed instructions are in the protocol body.

Diabetes and Hyperglycemia:

Cases of new onset of diabetes will be recorded as AEs. Clinical laboratories, including HbA_{1C} and glucose, will also be evaluated across treatment groups during this study and all ongoing studies to identify potential cases of new onset of diabetes.

Neurocognitive Events:

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs.

Clinical Endpoints:

Clinical endpoints will be monitored and adjudicated by an independent expert CEC for this study and other ongoing studies in the bempedoic acid program.

Routine cardiovascular monitoring will include review of cardiovascular AEs, SAEs, standard vital signs, and ECGs.

Further details on occurrence and monitoring are available in the Investigator's Brochure (IB).

Statistical methods:

Sample Size

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C.

[redacted]

[redacted]

Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy analyses, is defined as all randomized patients. The FAS is also known as the intention-to-treat (ITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received.

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of study medication. Patients in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

Primary Endpoint

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. Baseline LDL-C is defined as the mean of the LDL-C values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). The primary analysis will be that from the PMM, while the observed case analysis will be used as confirmatory. The PMM will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Imputed datasets will be analyzed using ANCOVA with the treatment and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. Approximately 200 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

Secondary and Tertiary Efficacy Endpoints

Secondary efficacy endpoints are also of interest for this study, in terms of controlling the overall Type I error rate, a gatekeeping or stepdown approach will be used to test the primary efficacy endpoint and then specific secondary efficacy endpoints sequentially in order to preserve the study-wise Type I error rate. The sequence for the stepdown procedure in this study is as follows:

1. Test the primary efficacy endpoint: percent change from baseline to Week 12 in LDL-C
2. Test the percent change from baseline to Week 24 in LDL-C
3. Test the percent change from baseline to Week 12 in non-HDL-C
4. Test the percent change from baseline to Week 12 in TC
5. Test the percent change from baseline to Week 12 in apoB
6. Test the percent change from baseline to Week 12 in hs-CRP

In this hierarchical testing structure, each hypothesis is tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. If the primary endpoint meets the criteria for statistical significance, then the percent change from baseline to Week 24 in LDL-C will be tested; and so forth.

For the remaining secondary efficacy endpoints and the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints, the p-values for those endpoints will be considered descriptive.

Percent change from baseline to Week 24 in LDL-C; change from baseline to Weeks 12 and 24 in LDL-C; percent change from baseline to Weeks 12 [redacted] in [redacted] non-HDL-C, [redacted] TC, apoB, and

hs-CRP will each be analyzed using ANCOVA with treatment group and patient type (primary prevention; secondary prevention) as factors and the relevant baseline as a covariate. Baseline for [redacted] non-HDL-C, [redacted] and TC will be defined as the mean of the lipid values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP will be defined as the predose Day 1/Week 0 (Visit T1) value. Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Only observed case data will be included in each analysis (no imputation will be performed for missing data). For each lipid parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For all continuous efficacy endpoints (percent change from baseline in LDL-C, [redacted] non-HDL-C, TC, [redacted] apoB, and hs-CRP; change from baseline in LDL-C; to Weeks 12 and 24, as appropriate), the ANCOVA assumption of normality will be assessed. If non-normality of the data is found at any time point for any parameter, either the data will be transformed so that it is normally distributed or a nonparametric test will be used instead of the planned ANCOVA.

Additional Post-randomization Adjunctive Triglyceride-lowering Therapy:

The number and percent of patients in each treatment group requiring additional (post-randomization) TG-lowering therapy will be summarized. The medications will be summarized by treatment group.

Safety Analyses

The summarization of AEs will include TEAEs. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group. These AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, coagulation, HbA_{1C}, glucose, and urinalysis; PE findings; vital signs; ECG readings; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each post baseline time point.

Hepatic Safety

For liver-associated enzymes and TB, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. Hy's law criteria ($\geq 3 \times$ ULN for either ALT or AST, with accompanying TB $>2 \times$ ULN in the absence of other known causes) will also be applied to the data; any potential Hy's law cases will be listed separately. For patients with Gilbert's disease, conjugated (direct bilirubin) will be used for the evaluation.

Musculoskeletal Safety

AEs of muscle-related symptoms will be summarized by treatment group. In addition, the number and percent of patients with abnormal CK values will be summarized.

Diabetes/Hyperglycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group.

Renal Safety

Baseline eGFR and values of CK will be summarized by treatment group and by baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms and will be performed by treatment group.

Clinical endpoints

Clinical endpoints using standardized definitions will be adjudicated by an independent blinded expert CEC for all ongoing Phase 3 studies in the bempedoic acid program. Investigator-reported clinical endpoints and adjudicated clinical endpoints will be summarized by event type and treatment group. Additional details regarding the clinical endpoints and their definitions will be included in CEC Charter.

Pharmacokinetics

Three pharmacokinetic (PK) samples will be collected. Plasma concentrations of bempedoic acid and its metabolite ESP15228 will be determined in patients who are receiving bempedoic acid, who have compliance ≥80%, and who have taken a dose of bempedoic acid within 2 days of the sample collection. All patients, site personnel, and study personnel will remain blinded to treatment assignment throughout the duration of the study. Personnel performing the bioanalytical analysis of bempedoic acid concentrations will be unblinded in order to assay the appropriate samples during the study. Plasma concentrations of bempedoic acid and ESP15228 will be summarized using descriptive statistics by time point.

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3. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACC	American College of Cardiology
ACL	Adenosine triphosphate-citrate lyase
ACS	Acyl-CoA synthetase
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
AHA	American Heart Association
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
apoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CETP	Cholesterol ester transfer protein
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
C_{max}	Time to peak maximum concentration
CMV	Cytomegalovirus
CNS	Central nervous system

Abbreviation	Definition
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CRO	Contract research organization
CTA	Computed tomography angiography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
EAS	European Atherosclerosis Society
EC	Executive committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESC	European Society of Cardiology
ETC-1002	Bempedoic acid
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A_{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-ABVivi	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A

Abbreviation	Definition
hr	Hour
HR	Heart rate
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LFT	Liver function test
LS	Least squares
LSM	Least squares mean
MACE	Major adverse cardiovascular event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MED ID	Medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NA	Not applicable
NLA	National Lipid Association

Abbreviation	Definition
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
PAD	peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PMM	Pattern mixture model
PT	Prothrombin time
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	Statin intolerant
siRNA	small interfering ribonucleic acid
SOC	System organ class
SP	Safety population
SUSAR	Suspected and unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal

Abbreviation	Definition
US	United States
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1. Overview of the Disease Under Study

Bempedoic acid (ETC-1002) is an inhibitor of adenosine triphosphate-citrate lyase (ACL) (adenosine triphosphate [ATP] citrate lyase), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. It is an oral first-in-class small molecule designed to lower low-density lipoprotein cholesterol (LDL-C) levels in patients with high cardiovascular risk unable to meet their treatment goals with currently available lipid-lowering therapies.

More people die annually from cardiovascular disease (CVD) than from any other disease. CVD remains the leading cause of death among Europeans, Americans, and other populations around the world (WHO 2015). In the United States (US), based on 2011 data, more than 2,150 Americans die from CVD per day, an average of 1 death every 40 seconds (Mozffarian 2015). The relationship between CVD and elevations in LDL-C is undisputed. Many clinical studies have demonstrated that lowering elevated levels of LDL-C reduces the risk of heart attacks, stroke, and death (Baigent 2010). More than half of the adult population has high cholesterol; therefore, lowering elevated LDL-C is a very important step in the battle against heart disease. It is also known that elevation of high-sensitivity C-reactive protein (hs-CRP; a measure of systemic inflammation) has been associated with increased cardiovascular (CV) risk (Bikdeli 2011; Vidula 2008), and lowering hs-CRP with statin therapy—independent of the level of LDL-C achieved with the statin treatment—significantly reduces recurrent coronary events (Ridker 2005). Given the evidence, hs-CRP is included as a risk indicator in the Reynolds Risk algorithm (Ridker 2007) and in clinical practice guidelines for the management of dyslipidemia (Jacobson 2014; Stone 2013). The Reynolds Risk score, which includes hs-CRP, has proved to be an excellent CV risk assessment tool (DeFilippis 2011).

The use of HMG-CoA reductase inhibitors, or statins, is one of the most important advances in the management of CVD, decreasing CV morbidity and mortality by approximately 25% in eligible patients (Joy 2009). However, tolerability is an important barrier to statin adherence. Muscle complaints, which encompass a range of conditions from myalgia to rare but life-threatening rhabdomyolysis, represent a major cause of statin discontinuation in clinical practice (Joy 2009). In addition, a range of other signs and symptoms may lead to discontinuation, including elevated liver enzymes, gastric upset, diarrhea, constipation, rash, headache, dizziness, mental confusion, forgetfulness, and erectile dysfunction (Eckel 2010). The statin intolerant (SI) patient population constitutes a major public health concern.

Guidelines now recommend very aggressive lowering of LDL-C in high-risk individuals to levels below 100 mg/dL and often under 70 mg/dL (Jacobson 2014) or reduction of ≥50% (Stone 2013). Worldwide, statins are used by tens of millions in order to achieve these aggressive lipid goals. Recent guidelines for the treatment of hypercholesterolemia are likely to further increase the number of patients taking statins, possibly to as many as 1 in 3 American adults. Consequently, as the number of statin-treated patients grows, the problem of statin intolerance will increase in importance as a public health concern. Current guidelines recognize that some patients develop intolerable side effects with statins. These guidelines recommend

patients be treated with the maximum-appropriate intensity of a statin that does not cause adverse effects (Stone 2013).

4.2. Overview of Bempedoic Acid

4.2.1. Mechanism of Action

Bempedoic acid is a first-in-class small molecule inhibitor of ACL, an enzyme upstream of HMG-CoA in the cholesterol biosynthesis pathway. Bempedoic acid is a prodrug that requires activation in liver to ETC-1002-coenzyme A (ETC-1002-CoA), which mediates competitive inhibition of ACL. Inhibition of ACL by ETC-1002-CoA decreases cholesterol synthesis in liver leading to increased LDL receptor (LDLR) expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002-CoA reduces LDL-C via the same pathway as HMG-CoA reductase inhibition by statins.

An important differentiating feature of bempedoic acid is that, unlike statins, it does not inhibit cholesterol synthesis in skeletal muscle. The enzyme required to convert bempedoic acid to ETC-1002-CoA is not present in skeletal muscle. Therefore, bempedoic acid is not anticipated to mediate the adverse effects associated with inhibition of biological intermediates within the cholesterol biosynthesis pathway in skeletal muscle; however, the safety of bempedoic acid and its metabolites regarding human skeletal muscle is not yet established.

4.2.2. Pharmacokinetics and Pharmacology

In both single- and multiple-dose studies, bempedoic acid is well absorbed (with a time to peak maximum concentration [C_{max}] of approximately <4 hours). The C_{max} of bempedoic acid and ESP15228 increased in proportion to increasing dose. The terminal elimination half-life ($t_{½}$) ranged from 15 to 27 hours for bempedoic acid and 20 to 33 hours for ESP15228.

In clinical drug-drug interaction studies, bempedoic acid 240 mg showed less than a 2-fold increase in the exposure of atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg, and rosuvastatin 10 mg in 2 statin drug-drug interaction studies (Studies 1002-007 and 1002-012). This increase was generally less pronounced when bempedoic acid 180 mg was administered with high dose statins (atorvastatin 80 mg, simvastatin 40 mg, pravastatin 80 mg, and rosuvastatin 40 mg) in Study 1002-037, suggesting that the combination is unlikely to alter safety profile of statins. No drug interaction occurred between daily bempedoic acid 180 mg and metformin in patients with type 2 diabetes mellitus (T2DM). A Phase 2 study evaluated and showed no effect of ezetimibe 10 mg on steady-state trough bempedoic acid plasma concentrations in 40 patients with hypercholesterolemia randomized to receive bempedoic acid plus ezetimibe (Study 1002-008). Results of a drug interaction study in 19 patients (16 evaluable for pharmacokinetics [PK]) with the oral contraceptive Ortho-Novum 1/35 in healthy women demonstrate no effect of daily bempedoic acid 180 mg on ethinyl estradiol or norethindrone exposure (Study 1002-017).

The results of the thorough QT/QTc (TQT) study (1002-022) showed no significant change in QTc. Following daily bempedoic acid 240 mg for 9 days, bempedoic acid does not prolong QT interval duration and has no clinically significant effect on heart rate and PR and QRS intervals.

4.2.3. Dose Selection

[redacted]

4.3. Nonclinical Experience

[redacted]

4.4. Clinical Experience

[redacted]

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

- To assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing LDL-C in statin intolerant patients with elevated LDL-C

5.1.2. Secondary Objectives

- To evaluate the effect of 24-week treatment with bempedoic acid 180 mg/day versus placebo on LDL-C
- To evaluate the effect of bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), hs-CRP, and apolipoprotein B (apoB) after 12 weeks of treatment
- To evaluate the 24-week safety and tolerability of bempedoic acid 180 mg/day compared to placebo

5.1.3. Tertiary Objective

[redacted]

5.2. Study Endpoints

5.2.1. Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C

5.2.2. Secondary Endpoints

1. Percent change from baseline to Week 24 in LDL-C
2. Percent change from baseline to Week 12 in non-HDL-C, TC, apoB, and hs-CRP
3. Absolute change from baseline to Weeks 12 and 24 in LDL-C

5.2.3. Tertiary Endpoints

[redacted]

5.2.4. Safety Endpoints

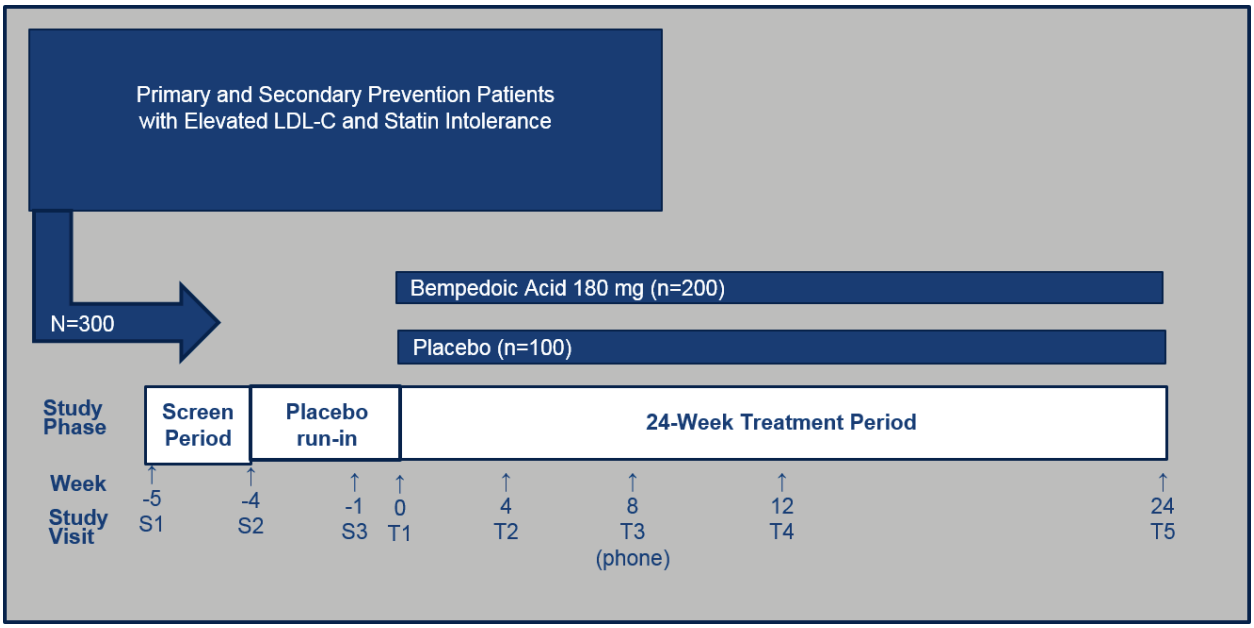
1. Patient incidence to TEAE
2. Safety laboratory values and vital signs
3. Cardiovascular event rates

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

The overall study design for 1002-046 is provided in Figure 1.

Figure 1: 1002-046 Study Design



6.2. Study Population and Selection

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 71 clinical sites in North America. Screening Week -5 (Visit S1) will be approximately 5 weeks prior to randomization. The time period between Visits S1 and S2 can be extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons. Eligible patients will return to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo study drug. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel regarding their eligibility status and considered screen failures. As necessary, for reasons of safety if a patient begins the run-in period but screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of AEs.

Approximately 300 patients with a history of SI will be stratified based on patient type (primary prevention; secondary prevention) and randomized at Week 0 (Visit T1) in a 2:1 ratio to receive either bempedoic acid 180 mg (n = 200) or matching placebo (n = 100) once daily for 24 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), and Week 24 (Visit T5). A phone visit will occur at Week 8 (Visit T3).

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety data from this and other ongoing Phase 3 studies of bempedoic acid. All clinical endpoints, including all major cardiac events (MACE) and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction (MI) (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions.

For details of study assessments, see the Schedule of Events in Section 8.3.

6.2.1. Inclusion Criteria

1. Provision of written informed consent must be obtained prior to any study-specific procedure.
2. Men and nonpregnant, nonlactating women. Women must be either:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      – ≥55 years, **or**
      – <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; or
   c. Women of childbearing potential must be willing to use 2 acceptable methods of birth control (unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:
      – oral, implanted, topical, or injectable birth control medications
      – placement of an intrauterine device with or without hormones
      – barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
      – vasectomized male partner who is the sole partner for this patient
      – true abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.

3. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -5 (Visit S1)
4. Fasting (minimum of 10 hours) calculated LDL-C at Week -5 (Visit S1)
   - Primary prevention ≥130 mg/dL (3.4 mmol/L)
   - Secondary prevention and/or heterozygous familial hypercholesterolemia (HeFH) ≥100 mg/dL (2.6 mmol/L)
   - All patients must have fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3)

   In the case of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor use, the patient must have received 3 stable doses. It is important that lipid values are measured at PCSK9i trough levels. Therefore, study visits should be scheduled in accordance with the patient's PCSK9i injection regimen so that measurement of lipid values for all visits occurs before the PCSK9i injection but not greater than 48 hours before the next scheduled PCSK9i injection. Patients who have discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least 4 months prior to Screening Visit S1.
5. Requiring statin therapy for the purpose of primary or secondary prevention of cardiovascular events.
   a. Primary Prevention patients must as a minimum have a history of requiring lipid-modifying therapy based on local guidelines (for example, American College of Cardiology [ACC]/American Heart Association [AHA] guidelines, European Society of Cardiology [ESC]/European Atherosclerosis Society [EAS] guidelines, Canadian Cardiovascular Society guidelines).
   b. Secondary prevention and/or HeFH patients must include those with a history of:
      – HeFH, defined by:
      – Genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 5) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 6).

        and/or

      – Coronary artery disease, defined by:
        ○ MI (either ST-elevation MI or non-ST-elevation MI) occurring greater than 90 days prior to screening (Week -5 Visit S1), **or**
        ○ Percutaneous coronary or surgical coronary revascularization, occurring greater than 90 days prior to screening (Week -5 Visit S1), **or**
        ○ Angiographic stenosis of >50% in a least 1 major coronary artery (native or graft vessel), as documented by selective coronary angiography or computed tomography angiography (CTA), **or**

- Symptomatic peripheral arterial disease (PAD), defined by:
  - Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index ≤0.9 performed by a vascular lab or angiogram (including CTA) showing ≥50% stenosis, **or**
  - Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening (Week -5, Visit S1), **or**
  - Abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring greater than 90 days prior to screening (Week -5, Visit S1), **or**
  - Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening (Week -5, Visit S1), **or**
- Cerebrovascular atherosclerotic disease defined by:
  - Ischemic stroke occurring greater than 90 days prior to screening (Week -5 Visit S1), **or**
  - Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram, occurring greater than 90 days prior to screening (Week -5 Visit S1).

6. Patient-reported SI defined as an inability to tolerate 2 or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued.

   Low-dose statin therapy is defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg.

   Please note that patients currently tolerating very-low-dose statin therapy (an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg) are considered to be intolerant to that low-dose statin. Patients may continue taking very-low-dose statin therapy throughout the study provided that it is stable (used for at least 4 weeks prior to screening, S1) and are taken at a consistent time each day.
7. Written confirmation by both patient and principal investigator that the patient is statin intolerant as defined above and aware of the benefit of statin use to reduce the risk of MACE including cardiovascular death.

6.2.2. Exclusion Criteria

1. Total fasting (minimum of 10 hours) TG ≥500 mg/dL (5.6 mmol/L at Week -5 (Visit S1).

   Note: A single repeat, fasting (minimum of 10 hours) of TG may be completed prior to initiation of the single-blind Run-in period. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.

2. Renal dysfunction or a glomerulonephropathy, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m2 at Week -5 (Visit S1).

   Note: A single repeat of eGFR may be completed between Visits S1 and S2. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

3. Body mass index (BMI) ≥50 kg/m^2
4. Recent (within 3 months prior to the screening visit [Week -5 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.
5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg measured according to local standards.

   Note: At the discretion of the investigator, the time between Visits S1 and S2 can be extended by 4 weeks for adjustments in blood pressure (BP) medications and/or additional assessment of BP, with the repeat assessment value used to determine eligibility. Alternatively, patients can be rescreened if BP status has changed.

6. Hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -5 (Visit S1).
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.
8. Liver disease or dysfunction, including:

   - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -5 (Visit S1).
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥1.2 × ULN at Week -5 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

   Note: At the discretion of the investigator, a single repeat of ALT, AST, and/or TB may be completed prior to randomization. For those patients who have a repeat ALT and/or AST, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.

9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption.
10. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Week -5 (Visit S1)
11. Persistent poor compliance or lack of tolerance with single-blind, placebo study drug (ie, ingesting <80% average of planned doses) assessed at the T1 visit prior to randomization.
12. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.
13. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
14. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other meds for chronic pain that have been stable, without evidence of abuse, and prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
15. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood transfusion, or major surgery with or without blood loss within 30 days prior to randomization.
16. Use of any experimental or investigational drugs within 30 days.
17. Previous enrollment in an Esperion bempedoic acid clinical study.
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Week -5 [Visit S1]),
    - Lomitapide or apheresis therapy (must be stopped at least 3 months prior to Week -5 [Visit S1]),
    - Red yeast rice extract and berberine-containing products must be stopped at least 2 weeks prior to Week -5 [Visit S1]),
    - Use of an investigational cholesterol ester transfer protein (CETP-I) within the last 2 years (except evacetrapib within the last 3 months).
    - Statins are prohibited at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg.

    Note: Patients can be on any available lipid-modifying therapy with the exception of the exclusions listed above as long as they have been stable on oral medications for 4 weeks prior to Screening Visit S1 and are taken at a consistent time each day.

19. Planned initiation or changes to the following drugs:
    - Hormone replacement (6 weeks prior to randomization)
    - Thyroid replacement (6 weeks prior to randomization)
    - Diabetes medications (4 weeks prior to randomization)
    - Obesity medication (4 weeks prior to randomization)
    - PCSK9 inhibitors: Patients who are currently on a stable commercially available PCSK9 inhibitor (alirocumab or evolocumab) must have had at least 3 doses prior to Visit S1. Patients who were previously (either investigational or commercial) on a PCSK9 inhibitor, must wait at least 4 months after last dose prior to screening (Week -5, Visit S1).
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
22. Pregnant, breastfeeding, or intending to become pregnant within 30 days after last dose of study drug.
23. Patients who have enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9 are excluded.
24. In patients taking very low dose statins, gemfibrozil is excluded per the co-administration prescribing instructions.

6.3. Patient Identification, Randomization, and Blinding

Patient identification numbers will be assigned sequentially by interactive web response system (IWRS) at the time of informed consent during the screening module transaction.

For patients who satisfy all entry criteria and complete the 5-week screening period, randomization will occur at Week 0 (Visit T1). Patients will be stratified on primary prevention or secondary prevention and randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- bempedoic acid 180 mg or
- matching placebo

The Sponsor, all clinical site personnel (Investigator, pharmacist, etc), and other vendor personnel will be blinded to the treatment group for each patient. Patients will also be blinded to the treatment they receive.

Blinding of treatment must be maintained for all patients unless, in the opinion of the Investigator, the safety of the patient may be at risk. Only under the rarest of circumstances should the Investigator consider breaking the blind and only when medical/supportive care cannot be provided without determining if the patient is receiving active drug treatment. In the event that the blind needs to be broken prior to completion of the study, the Investigator should contact the appropriate Medical Monitor by telephone. If the blind must be broken prior to

consultation with the Medical Monitor, contact must be made within 24 hours of breaking the blind. At the initiation of the study, the clinical site will be instructed on procedures for breaking the blind via the IWRS. In all cases of breaking the blind, the Investigator must document in the patient's medical record the date, time, and reason for breaking the blind, and the names of personnel involved.

Limited vendors (ie, the bioanalytical laboratory and other vendor personnel, if any, that are responsible for PK analysis) will have access to the randomization codes to facilitate PK analytical work, and will be instructed to not communicate in any manner information associated with treatment assignment to any personnel at the clinical site, the Sponsor, or contract research organization (CRO).

Post-randomization values for individual laboratory measures for LDL-C, TG, TC, HDL-C, non-HDL, apoB, and hs-CRP, including any plasma concentration of bempedoic acid and its metabolite that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, and CRO.

7. INVESTIGATIONAL MEDICINAL PRODUCT

7.1. Investigational Medicinal Product Supply and Control

The Sponsor will supply the investigational medicinal product (IMP) for this study. The IMP for this study includes bempedoic acid (180-mg film-coated tablets) and matching placebo (film-coated tablets). IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study.

The medication identification (MED ID) number (an identifier on the study drug packaging) will be obtained via IWRS and used to select placebo study drug for the single-blind placebo run-in period and double-blind IMP for the treatment period from available clinical supplies at the clinical site.

A 35-day supply of single-blind placebo drug will be dispensed one time at Week -4 (Visit S2) for the 4-week placebo run-in period of the study. Double-blind IMP will be dispensed in 100 day supply increments (one 100-day supply bottle) to patients by appropriate clinical site personnel at Week 0 (Visit T1), and Week 12 (Visit T4).

Please see Pharmacy Manual for detailed storage requirements and management instructions.

7.2. Administration of Investigational Medicinal Product

Patients will be instructed to ingest, placebo study drug starting at Visit S2 for the duration the placebo run-in period and the IMP starting at Visit T1 for the duration of treatment period orally once daily (once every 24 hours) at approximately the same time each day with water. IMP may be taken with or without food. On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed.

If the patient fails to take IMP, details describing the reasons for nondosing should be documented in the patient's medical records and eCRF. Extra IMP (7 extra days per bottle) is provided and can be used, if needed, prior to the next visit or to replace a dose of IMP that cannot be used because it is lost or damaged.

Table 1: Investigational Product

	Investigational Medicinal Product	
Product Name:	Bempedoic acid	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure[a]:	100-count bottle with screw on, child-proof cap	35- or 100-count bottle (depending upon visit) with screw on, child-proof cap
Route of Administration:	Oral, once per day, with or without food	Oral, once per day, with or without food
Physical Description:	[redacted]	

[a] A 100-day supply of study drug will be included in the 100-count bottle and a 35-day supply of single blind placebo will be included in the 35-count bottle.

7.3. Concomitant Medications

Patients will be questioned about their concomitant medication use at each clinic visit. All concomitant medication taken chronically or intermittently during the study must be recorded with indication, total daily dose, and start and stop dates of administration.

The Prior/Concomitant electronic case report form (eCRF) will be used to record medications, herbal remedies, vitamins, other supplements, and over-the-counter medications taken within 3 months prior to screening (Week -5 Visit S1) and during the study.

7.3.1. Lipid-Regulating Medications and Supplements

Patients are allowed to continue their background lipid-lowering therapy during this study as long as the drugs and doses are stable for 4 weeks prior to screening (at least 3 doses are required for PCSK9 inhibitors). Use of fibrates must be stable at least 6 weeks prior to screening (Week -5 Visit S1). Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies and include:

Statins

Patients currently tolerating very-low-dose statin therapy are also considered to be statin intolerant and may continue taking that statin/dose throughout the study provided that it is stable (used for at least 4 weeks prior to screening) and well tolerated.

Average daily dose:

- rosuvastatin <5 mg,
- atorvastatin <10 mg,
- simvastatin <10 mg,

- lovastatin <20 mg,
- pravastatin <40 mg,
- fluvastatin <40 mg, or
- pitavastatin <2 mg)

Selective cholesterol and/or bile acid absorption inhibitors

- Cholestyramine/Colestryamine (Questran®, Questran Light®, Prevalite®, Locholest®, Locholest® Light)
- Colestipol (Colestid®)
- Colesevelam hydrochloride (Welchol®,Cholestagel®)
- Ezetimibe (Zetia®, Ezetrol®)

Fibrates

- Fenofibrate (Antara®, Lofibra®, Tricor®, Triglide™, Lipantil®, Supralip®)*
- Bezafibrate (Bezalip®)
- Ciprofibrate (Modalim®)

* Note that gemfibrozil (lopid®) is exclusionary in patients taking a very low dose statin as per co-administration prescribing instructions.

PCSK9 inhibitors

- Alirocumab (Praluent®)
- Evolocumab (Repatha®)

Other

- Niacin (Niaspan®, Niacor®, Slo-Niacin®)
- Combination statin products must be at or below the above listed average daily statin dose.

7.3.2. Prohibited Medications

The use of the following medications and/or supplements are prohibited during the study.

- Statins at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg
- New or planned dose changes of systemic corticosteroids.

  Note: Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks from Visit S1). Topical and inhaled steroids are allowed.
- Red yeast rice (monacolin K) extract and Berberine-containing products must be discontinued 2 weeks prior to screening (Week -5, Visit S1).

- Lomitapide or apheresis therapy within 3 months to screening (Week -5, Visit S1).
- Mipomersen within 6 months to screening (Week -5, Visit S1).
- CETP-I within the last 2 years to screening (Week -5, Visit S1) except for Evaceptrapib within the last 3 months to screening (Week -5, Visit S1).
- New or planned anti-arrhythmia medication(s) within 3 months to screening (Week -5, Visit S1).
- Previous enrollment into a study of an experimental siRNA of PCSK9 or use of any other experimental or investigational drugs within 30 days to screening (Week -5, Visit S1).
- Gemfibrozil in patients taking a very low dose statin as per co-administration prescribing instructions.

7.3.3. Allowable Medications

Patients must be on stable concomitant medication regimen(s) for the following medications and/or supplements:

- Hormone replacement therapy within 6 weeks of randomization
- Thyroid replacement therapy within 6 weeks of randomization. Diabetic medication(s) within 4 weeks of randomization.
- Obesity medication(s) within 4 weeks of randomization.
- Oral lipid-modifying therapy within 4 weeks to screening (Week -5, Visit S1).
- PCSK9 inhibitors (alirocumab or evolocumab) if at least 3 doses prior to Visit S1. Patients who were previously (either investigational or commercial) on a PCSK9 inhibitor, must have discontinued 4 months prior to screening (Week -5, Visit S1)
- Hypertensive medication(s) within 2 weeks prior to randomization.
- Hypertriglyceridemia medication(s) within 4 weeks prior to screening (Week -5, Visit S1) with the exception of fibrates that are within 6 weeks prior to screening (Week -5, Visit S1)

7.4. Patient Lifestyle and Dietary Guidelines

Patients will be counseled to follow a lipid-lowering diet as per local or regional guidelines and should be encouraged (as able) to participate in a regular exercise program throughout the study.

7.5. Treatment Compliance

Screening Compliance

No study medication treatment will be given during the Screening period; therefore, compliance will not be assessed.

Placebo Run-In Adherence to Study Medication

At visits Week -1 (S3) and Week 0 (T1), designated clinical site staff will assess patient study drug compliance by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. If at the Week -1 (S3) visit the patient has not taken all doses of study drug(s) as instructed, the patient will be queried for a reason, findings will be documented, and the patient will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. If at the T1 visit, the average study drug compliance from the placebo run-in period is <80%, or if the patient experiences an adverse event related to the run-in single blind placebo, the patient will not go onto randomization.

Treatment Period Adherence to Study Medication and Procedures

At each patient visit during the treatment period, designated clinical site staff will assess patient study drug compliance by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. If the patient has not taken all doses of study drug(s) as instructed, the patient will be queried for a reason, findings will be documented, and the patient will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. Patients demonstrating poor adherence will continue to be counseled on the importance of carefully following all dosing instructions, but will not be removed from the study.

8. STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

8.1. Informed Consent

The patient must be adequately informed of the nature and risks of the study and understand the informed consent document (ICD). No study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

8.2. Confirmation of Statin Intolerance (SI)

The investigator is responsible for reviewing the patient's available medical records and assessing the patient for SI. This will include a review of statin use history.

Both the patient and the investigator will sign a form confirming that that the patient is statin intolerant. Within this form, the patient will acknowledge an understanding that they are at high risk for experiencing a heart attack or stroke and death and that using a statin would reduce that risk; however, they are not taking a statin because of intolerable side effects that started or increased during statin therapy and resolved or improved when statin therapy was discontinued. Within the same form, the investigator will confirm that the patient is unable to tolerate statin therapy (except possibly at very low average daily doses of atorvastatin <10 mg, fluvastatin <40 mg, lovastatin <20 mg, pravastatin <40 mg, pitavastatin <2 mg, rosuvastatin <5 mg, or simvastatin <10 mg) based on review of the medical history and discussion with the patient.

Documentation of prior statin use will be based on patient recall and copies of relevant medical records and pharmacy records if readily available. If investigator is unable to assess prior statin use due to poor patient recall and/or lack of relevant medical records, and if appropriate according to local medical practice, documentation of contact with primary care physician regarding prior statin use should be obtained. At minimum, there will need to be documentation for the name of 2 statins and the dose of at least 1 statin attempted at low dose to ensure inclusion criteria is met. All available prior statin use history will be recorded in the eCRF. Additionally, the basis for the investigator's confirmation of the patient's SI will be noted in the eCRF.

8.3. Procedures and Schedule of Assessments

The study will be conducted as outlined in the following sections. Table 2 summarizes the study assessments at each study visit for patients enrolled in this study, followed by an overview of assessments by visit in Sections 8.3.1-8.3.8 . Further details of the assessments are provided in the Study Operations Manual.

Table 2: Schedule of Events (Subject Visit Schedule)

Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28 ±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169 ±7**
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
Statin Intolerance Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight[4]	X			X			X	X
Height/BMI	X							
12-Lead ECG[5]			X					X
Vital Signs[6]	X	X	X	X	X		X	X
Serology[7]	X							
Serum Pregnancy[8]	X							
Urine Pregnancy[9]				X				
TSH	X							
Clinical Safety Labs[10]	X		X	X	X		X	X
Basic Fasting Lipids[11]	X		X	X	X		X	X

Table 2: Schedule of Events (Subject Visit Schedule)

Visit	S1[1,2]	S2	S3	T1	T2	T3/phone	T4	T5/EOS[3]
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28 ±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169 ±7**
HbA_{1C}	X			X			X	X
PK sample					X		X	X
apoB				X			X	X
hs-CRP				X			X	X
Diet and exercise counseling[12]	X	X	X	X	X	X	X	
Establish Patient Eligibility		X		X				
Randomization				X				
IWRS Contact[13]	X	X		X			X	X
Single-blind Drug Dispensing		X						
Double-blind Drug Dispensing				X			X	
Drug Return/Compliance			X	X	X		X	X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visits, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs).

[1] An optional fasting (minimum of 10 hours) TG assessment MAY be completed between Visits S1and S2 (prior to starting single-blind medication) if patient fails to meet TG criterion at Visit S1. The repeat value will be used to determine eligibility.

[2] A recheck of blood pressure may be completed between Visits S1 and S2 if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (diastolic blood pressure [DBP] and/or systolic blood pressure [SBP]) do not meet exclusionary values. Repeat labs may be completed between Visit S1 and Visit S2 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

[4] Body weight will be measured while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[5] Single 12-lead ECG will be performed prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

[7] Serology for HbsAg, HCV-ABVivi.

[8] Pregnancy test completed in women of child-bearing potential only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

[9] Urine pregnancy test completed in women of child-bearing potential only just prior to randomization.

[10] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. A coagulation panel will be completed for all patients at Week -5 (Visit S1). A coagulation panel will be completed only for patients on vitamin K antagonists at Day 1 (Visit T1) and 3 to 5 days later. For these visits, the sample may be analyzed at either the central or a local lab. Please refer to laboratory manual for detailed schedule of tests.

[11] Basic fasting (minimum of 10 hours) lipids include total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides.

[12] Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

[13] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

8.3.1. Screening Week -5 (Visit S1; Day -35 ± 7 days)

The screening period will begin with a screening visit that will occur approximately 5 weeks prior to randomization. Visit S1 will allow the investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 8.1), the patient will undergo the following assessments and procedures at Visit S1:

1. Demographics
2. Clinically relevant medical history
3. Confirmation of statin intolerance and completion of confirmation forms
4. Prior and concomitant medication review
5. Review of all inclusion/exclusion criteria that can be assessed at this time
6. Height (cm), and weight (kg)
7. BMI
8. Vital signs
9. Diet and exercise counseling
10. Central clinical laboratory evaluations:
    - TSH
    - Coagulation
    - Hematology, blood chemistry, and urinalysis
    - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
    - HbA_{1C}
    - Serology (including HbsAg, hepatitis C virus [HCV] antibody
    - Serum pregnancy test in women of child-bearing potential only
    - FSH when required
11. Contact IWRS to register the patient which includes entering whether the patient fits the definition of primary prevention or secondary prevention. The IWRS system will be designed to ensure correct definitions of primary and secondary prevention are applied for purposes of stratification.

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their allowed therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion, other than those that can be repeated, are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

The screening period (between Visits S1 and S2) can be extended an additional 4 weeks if needed to adjust background therapy or other reasons.

Patients who are considered to be screen failures due to not meeting stability requirements for a condition or concurrent medication may be considered for rescreening after consultation with the Sponsor (or designee). These patients must be re-consented, re-registered in the IWRS, and will have a new patient ID number assigned.

8.3.2. Screening Week -4 (Visit S2; Day -28 ±3)

The single-blind run-in period for placebo begins at this visit. After the patient's eligibility is established, the patient will undergo the following assessments and procedures at Visit S2:

1. Concomitant medication review (ongoing)
2. Assess AEs, serious adverse events (SAEs), and potential clinical endpoints (starting from signing the informed consent document)
3. Physical examination (PE)
4. Vital signs
5. Diet and exercise counseling
6. Dispense single-blind placebo and ingestion of first dose. Provide dosing and storage instructions
7. IWRS Contact

8.3.3. Screening Week -1 (Visit S3; Day -7 ±3)

The patient will undergo the following assessments and procedures at Visit S3:

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints (starting from signing the informed consent document)
3. 12-lead electrocardiogram (ECG)
4. Vital signs
5. Central clinical laboratory evaluations:
    - Hematology, blood chemistry, and urinalysis
    - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG). LDL-C value must be ≥70 mg/dL
6. Diet and exercise counseling
7. Study drug compliance assessment

8.3.4. Week 0 (Visit T1; Day 1)

Prior to scheduling Visit T1, review the screening clinical results to determine whether the patient continues to meet lab eligibility criteria. At Visit T1, determine whether the patient was adherent with placebo treatment during the run-in period (average of ≥80% adherence required)

and had no issues with tolerability of run-in period study medication. Patients with intolerable side effects, including but not limited to muscular skeletal pain, will be run-in failures.

If the patient has met all inclusion criteria and none of the exclusion criteria, the patient may be randomized into the double-blind treatment period. Patients who fail to meet all entry criteria after initiation of single-blind placebo run-in are considered to be run-in failures and will not be randomized.

Patients are considered randomized once all eligibility criteria are confirmed and IWRS is contacted with confirmation of patient randomization on the day of first dose.

The patient will undergo the following assessments and procedures at Day 1 (Visit T1):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints
3. Return of unused single-blind placebo and assessment of dosing adherence
4. Review inclusion/exclusion criteria to establish patient eligibility
5. Weight
6. Vital signs
7. Central clinical laboratory evaluations:
    - Coagulation in patients on vitamin K antagonists (return 3-5 days after Visit T1 for repeat coagulation). Coagulation samples for this visit may be analyzed at the central or local lab.
    - Hematology, blood chemistry, and urinalysis
    - apoB
    - hs-CRP
    - HbA_{1C}
    - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
8. Urine pregnancy in women of childbearing potential only prior to randomization.
9. Diet and exercise counseling
10. IWRS contact to randomize patient and assign bottle number(s) for double-blind study drug
11. Dispense double-blind study drug and ingestion of first dose and provide dosing and storage instructions

8.3.5. Treatment Week 4 (Visit T2; Day 29 ±3 days)

Patients will undergo the following assessments and procedures at Week 4 (Visit T2):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints

3. Weight
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
   - PK Sample prior to dose
6. Return of study drug; assessment and recording of dosing adherence
7. Re-dispense IMP container from Visit T1 to patient for continued dosing and provide dosing and storage instruction.

Note: If the patient discontinues at any scheduled visit after T1, or between study visits, please proceed to Section 8.4.1 for detailed instructions.

8.3.6. Treatment Week 8 Phone Call (Visit T3; Day 57 ±3 days)

Patients will undergo the following assessments via telephone at Week 8 (Visit T3):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints
3. Diet and exercise counseling
4. Assessment of study drug dosing adherence

Note: If the patient discontinues at or between study visits, please proceed to Section 8.4.1 for detailed instructions.

8.3.7. Treatment Week 12 (Visit T4; Day 85 ±3 days)

Patients will undergo the following assessments and procedures at Week 12 (Visit T4):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints (ongoing)
3. Weight
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - apoB
   - hs-CRP
   - HbA_{1C}
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
   - PK Sample before dose

6. Diet and exercise counseling
7. Return of study drug; assessment and recording of dosing adherence
8. IWRS contact to obtain new MED ID numbers for double-blind study drug
9. Dispense double-blind study drug and provide dosing instruction

Note: If the patient discontinues at any scheduled visit after T1, or between study visits, please proceed to Section 8.4.1 for detailed instructions.

8.3.8. Treatment Week 24/EOS (Visit T5; Day 169 ±7 days)

Patients will undergo the following assessments and procedures at Week 24 (Visit T5):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints (ongoing)
3. Weight
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - apoB
   - hs-CRP
   - HbA_{1C}
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
   - PK Sample before dose
6. Return of study drug; assessment and recording of dosing adherence
7. IWRS contact to terminate the subject or register completion
8. Physical Exam
9. 12-Lead ECG

8.4. Early Withdrawal from Study or Treatment

Patients who withdraw from study drug prior to Week 24 (Visit T5) for any reason will be asked to continue to be followed for safety assessments, including basic fasting lipids, at clinic visit following the protocol-specified visit schedule (see Section 8.3).

Patients who temporarily withdraw from study drug prior to Week 24 (Visit T5) for any reason may restart study drug providing that 1) the patient and the investigator are in agreement regarding this course of action, 2) the patient has been off of study drug for 4 weeks or less; and 3) study drug can be started as soon as possible. For cases where the patient has been off of study drug for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting study drug.

Patients who do not wish to continue to return to the clinic for safety assessments will be asked to participate in phone calls from the site at protocol-specified visits (see Section 8.3), or at a minimum at 24 weeks, to collect information on AEs, concomitant medications, and current health status.

The patient's decision to participate in the clinical study is voluntary. Patients may refuse to continue in the study and/or withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled.

It is the right and duty of the Investigator to interrupt the treatment of any patient whose health or well-being may be threatened by continuation in this study. Such patients should be withdrawn from the study and should not be continued under a modified regimen.

Patients who are withdrawn from the study may not re-enter. The reasons for withdrawal from this study or treatment may include:

- Patient's withdrawal of consent
- Failure to comply with the protocol
- Lost to follow-up
- Illness, condition, or procedural complication (including AEs) affecting the patient's ability to participate or requiring prohibited medication
- The Sponsor or Investigator terminates the study
- In the Investigator's judgment, it is deemed in the best interest of the patient to discontinue his/her participation in the study
- Any other reason

If a patient is lost to follow-up, every reasonable effort must be made by the clinical site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

8.4.1. Procedures for Early Withdrawal

If a patient withdraws or is removed from the study for any reason, all "End of Study" procedures should be completed. Reason for withdrawal, date of the discontinuation, and date of the last dose of study drug should be recorded in the appropriate section of the eCRF. Additionally, the discontinuation visit date must be registered in IWRS. Study drug assigned to the withdrawn patient may not be assigned to another patient.

All effort should be made to have each patient complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed.

Patients choosing to withdraw from the study early should be encouraged to return for all study scheduled clinic visits even if they are no longer taking IMP. Patients who withdraw from all aspects of the study will be asked to consent to clinical visits or phone calls for safety assessments, including AEs, concomitant medication, and current health status through Week 24 (Visit T5). Subjects who are unwilling to return for clinic visits should return for an end of study visit (Visit T5).

8.4.2. Patients Lost to Follow-Up

A patient would be considered potentially lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Refer to the Retention Guide for additional details. Vital status will be collected within legal and ethical boundaries during the study closeout period. If vital status is determined, the patient will not be considered lost to follow-up.

8.4.3. Discontinuation of Study Sites or the Study

The Sponsor may suspend enrollment or discontinue a site at any time. A written statement will be provided to the Investigator, the IRB or IEC, and regulatory authorities, if required.

Possible reasons for site discontinuation include, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality
- Inaccurate or incomplete data collection on a chronic basis
- Falsification of records
- Failure to adhere to the protocol
- Lack of study oversight by the Principal Investigator and/or designee

If any serious or nonserious AEs have occurred at such a clinical site, all documentation relating to the event(s) must be obtained.

The Sponsor in consultation with the Executive Committee (EC) Chair will retain responsibility for discontinuation of the study. The study will be discontinued if necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

Discontinuation of the study may be based on a recommendation from the DMC. The criteria that the DMC will follow to recommend early termination the study will be described in the DMC Charter.

8.5. Overdose

There is no specific antidote for an overdose of bempedoic acid. Management of an overdose should be focused on the treatment of symptoms. These symptoms should be managed according to current standards of care with appropriate supportive measures. Also discontinuation of study drug should be considered, based on medical judgement.

9. ASSESSMENT OF EFFICACY

9.1. Efficacy Parameters

After randomization, patients will return to clinic/or have phone contact with the clinic every 4 to 12 weeks for a total of 24 weeks. Clinical laboratory samples will be collected and analyzed for basic lipid parameters at each visit.

9.2. Clinical Efficacy Laboratory Tests

Blood draws for efficacy (not safety) must meet the criteria below. If these criteria have not been met, efficacy blood samples will NOT be collected. **If these criteria can be met by rescheduling the clinic visit (within 3 days), efficacy blood samples will be collected at the rescheduled clinic visit only.**

- Blood samples will be drawn after a minimum 10-hour fast (water is allowed), and
- Patients will be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in Table 3. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping as well as monitoring and management of abnormal laboratories are described in Section 10.1.6.

When ECG, vital signs, and laboratory samples are to be collected at the same time point, ECG and vital sign measurements will precede laboratory sample collection.

Table 3: Clinical Efficacy Laboratory Tests

Clinical Laboratory Test	Clinical Laboratory Test
Basic Lipid Parameters • Total cholesterol (TC) • low-density lipoprotein cholesterol (LDL-C) and non-HDL-C [redacted]	Other Parameters • High-sensitivity C-reactive protein (hs-CRP) • Apolipoprotein B (apoB)

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

At all clinic visits, investigators will review all safety information including vital signs, AEs, concomitant medications, and ECG reports and will ensure that the collected data are recorded into the appropriate eCRF. Additionally, clinical laboratory samples will be collected and sent for analysis and the investigator will review the results to ensure continued patient safety while participating in the study.

10.1.1. Demographic/Medical History

Demographic data and a complete medical history will be obtained from the patient. For medical history, conditions that are relevant and/or clinically significant should be captured with at least a start date (month and year) and whether the condition is ongoing or resolved. All surgeries regardless of date should be reported.

10.1.2. Vital Signs

Vital signs will include DBP and SBP as well as heart rate.

The patient should sit quietly for 5 minutes prior to collection of vital signs. At all time points, vitals will be collected prior to blood collection. Blood pressure and heart rate will be measured using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper arm. If a fully automated machine is not available, BP may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study. The patient should be in a seated position with feet touching the floor. Patients should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on the ground, and their arms bared and supported at heart level. At each clinic visit, 2 BP measurements will be collected at least 5 minutes apart.

10.1.3. Weight, Height, and Body Mass Index

Weight will be measured on a calibrated scale while fasted, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

Height will be measured using standard clinic procedures.

BMI will be calculated using the formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight in kg} / (\text{height in meters})^2$$

10.1.4. Physical Examination

PEs will include an assessment of the following:

- General appearance
- Skin
- Eyes, ears, nose, and throat
- Head and neck
- Extremities
- Musculoskeletal examination
- Respiratory examination
- Cardiovascular assessment, including rhythm and presence of cardiac abnormalities
- Abdominal examination
- Neurologic examination including documentation of the presence of abnormalities in mental status and motor and sensory function
- Any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences

Documentation of the PE findings will be included in the source documentation at the clinical site. Significant findings noted at Visit S2 will be recorded on the Medical History/Current Medical Conditions page of the eCRF. Only changes from Visit S2 physical examination findings (or other unscheduled physical exams performed after informed consent but prior to randomization) that meet the definition of an AE will be recorded on the AE page of the eCRF.

Note: Additional information will be collected regarding muscle-related AEs. See Section 10.2.11.3.3.

10.1.5. Electrocardiogram

ECG collection will be preceded by a 10-minute rest time during which the patient will remain in the supine position. ECGs will be collected prior to blood collection. ECGs will be assessed using machine readings and physician review.

10.1.5.1. Monitoring and Management of Abnormal Electrocardiograms

If a clinically significant ECG abnormality not present at baseline (screening) is determined by the Investigator to be related to study drug, the abnormality will be discussed with the Sponsor personnel or the authorized Medical Monitor, and followed and evaluated with additional tests (if necessary) until the underlying cause is determined or the event is brought to an acceptable resolution. Additional clinical and laboratory information will be collected and carefully documented in order to better characterize the ECG abnormality and rule out alternative causes. ECG findings determined to be a clinically significant change from baseline should be reported as an AE regardless of causality.

Unscheduled ECG assessments will be completed at the discretion of the Investigator.

10.1.6. Clinical Laboratory Tests

10.1.6.1. Laboratory Parameters (Safety)

Patients will be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in Table 3-Table 4. Collection schedule, schedule of laboratory parameters by visit, and instructions are in the Clinical Laboratory Manual provided by Central Laboratory.

Table 4: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %)	Blood Chemistry (serum, fasting) • Albumin (Alb) • Alkaline phosphatase (Alk-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen • Urine Pregnancy in females of child bearing potential	

Table 4: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Coagulation – all patients at Visit S1; only in patients receiving vitamin K antagonists at Visit T1 and 3 to 5 days post Visit T1 using local or central lab • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) • Serum pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) • Thyroid-stimulating hormone (TSH)	Additional samples • Hemoglobin A_{1C} (HbA_{1C})

10.1.6.2. Clinical Laboratory Tests (PK)

A PK blood sample will be collected prior to dosing at Visits T2, T4, and T5.

Patients will be in a seated position during the blood collection. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping are described in Section 10.1.6.3.

10.1.6.3. Sample Collection, Storage, and Shipping

Clinical laboratory and PK samples will be collected by appropriate clinical site personnel and then shipped according to a separate laboratory manual provided by the Central Laboratory. Samples will be processed by the Central Laboratory, and PK samples will be forwarded to the Bioanalytical Laboratory for analysis.

10.1.6.4. General Monitoring and Management of Abnormal Clinical Labs

It is the Investigator's responsibility to review the results of all laboratory tests as they become available and to sign and date the report to document their review. For each laboratory test outside of the laboratory normal range, the Investigator needs to ascertain if this is a clinically significant change from baseline for the individual patient, with baseline defined as the last value or observation before the first dose of study drug. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the patient, the Investigator should determine if it qualifies as an AE, and if yes, an appropriate eCRF will be completed. An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality.
- Intervention for management of the abnormality is required.
- At the discretion of the investigator should the abnormality be deemed clinically significant.

All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause or resolution. Adverse events of special interest (AESI) monitored by clinical laboratories are discuss in the section on AESI (Section 10.2.11).

10.1.6.5. Total Blood Volume of Clinical Laboratory Samples

The total number of venipunctures and total volume of whole blood collected during the study will be limited to that needed for safety monitoring, efficacy, biomarker assessment, and genetic analysis. Total whole blood volume collected over the study duration is not to exceed approximately 250 mL for each patient.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, including control, and which does not necessarily have a causal relationship with treatment.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug
- TEAEs are defined as AEs that begin or worsen after the first dose of study drug
- Adverse drug reaction (ADR; see Section 10.2.2)

10.2.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR. “Responses” to a medicinal product means that a causal relationship

between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

10.2.3. Reporting

All AEs occurring during the course of the study (starting from signing informed consent to study completion or discontinuation) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the Investigator through 30 days following the last dose of study drug. Beginning with Visit S2 (Week -4), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Any SAE that occurs from the time of ICF through 30 days following the last dose of study drug should be reported to the Sponsor per Section 10.2.7.4.

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 AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure.

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

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs. 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. 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. Any abnormal test that is determined to be an error does not require reporting as an AE.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. For each AE, the following information will be recorded:

- Description of the event (eg, headache)
- Date of onset
- Date of resolution (or that the event is continuing)
- Action taken as a result of the event
- Seriousness of the event
- Severity of the event
- Outcome of the event

- Investigator's assessment of relationship to study drug.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever, elevated WBC, cough, abnormal chest x-ray, etc, can all be reported as "pneumonia").

The Investigator will carefully evaluate the comments of the patient and the response to treatment in order that he/she may judge the true nature and severity of the AE. The question of the relationship of AEs to study drug administration should be determined by the Investigator or study physician after thorough consideration of all facts that are available.

Additional information will be collected regarding muscle-related AEs that may include, but may not necessarily be limited to, a muscle-related questionnaire, with questions regarding type of muscle-related symptoms, location of the muscle-related AE, and potential cause of the muscle-related AE.

10.2.4. Severity of Adverse Events

It is the Investigator's responsibility to assess the intensity (severity) of an AE.

The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

- Mild: Events are usually transient and do not interfere with the patient's daily activities
- Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe: Events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

Note: A severe AE need not be serious and an SAE need not, by definition, be severe.

10.2.5. Relationship

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge.

It is the Investigator's responsibility to assess the relationship between the study drug and the AE. The degree of "relatedness" of the AE to the study drug may be described using the following scale:

- Not Related: No temporal association and other etiologies are likely the cause
- Unlikely: While cannot be definitively ruled as not related to IMP, a causal association is remote, and other etiologies are more likely to be the cause. For reporting and summarization, events assessed as "Unlikely" to be related to IMP will be considered as "Not Related" to IMP for regulatory reporting purposes.

- Possible: Temporal association, but other etiologies are likely the cause. However, involvement of the study drug cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the study drug is discontinued.
- Definite: Established temporal association with administration of the study drug with no other more probable cause. Typically, the event should resolve when the study drug is discontinued and recur on re-challenge.

10.2.6. Monitoring and Follow-up of Adverse Events

Patients having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. All follow-up results are to be reported to the Sponsor personnel or the authorized Medical Monitor. Any actions taken and follow up results must be recorded either on the appropriate page of the eCRF or in appropriate follow-up written correspondence, as well as in the patient's source documentation. Follow-up laboratory results should be filed with the patient's source documentation.

For all AEs that require the patient to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at appropriate intervals until final resolution, stabilization of the event(s), or until the patient is lost to follow-up or dies.

Patients with AEs that are ongoing at study completion or study withdrawal must be followed until resolution or for 30 days after the last study visit, whichever comes first (see Section 8.3).

10.2.7. Treatment-Emergent Adverse Event

TEAE are defined as AEs that begin or worsen after the first dose of study drug.

10.2.7.1. Definition of Serious Adverse Event

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Results in death
- Is life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- An important medical event

NOTE: Hospitalization is defined as a formal inpatient admission. This will not include admissions under "23-hour Observational Status", an Emergency Room visit without hospital admission or an Urgent Care visit and therefore, such events will not be recorded as an SAE under this criterion, nor will hospitalization for an elective or outpatient procedure scheduled or planned before signing of informed consent. However, unexpected complications that occur

during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Important medical events that may not result in death, be life threatening, or require hospitalization 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 in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Any clinical endpoints that meet SAE criteria will be reported as SAEs. The CEC will adjudicate clinical endpoints in a blinded fashion, but the DMC will review clinical endpoints and SAEs in an unblinded fashion.

10.2.7.2. Definition of Serious Adverse Event Events or Outcomes not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Preplanned or elective hospitalization including social and/or convenience situations (eg, due to inclement weather)
- Overdose of either Esperion study drug or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page

10.2.7.3. Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the central (or local where appropriate) laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. For criteria of reporting abnormal lab values as AE, see Section 10.1.6.4.

10.2.7.4. Reporting of Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following last dose of study drug, must be reported by the Principal Investigator or designee to the Safety designee within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. All SAEs that the Investigator considers related to study drug that occur after the 30-day follow-up of the study period must be reported to the Sponsor.

To report the SAE, complete the SAE information in the clinical EDC database within 24 hours of becoming aware of the occurrence. Additional information, such as diagnostic test results or hospital discharge summary can be sent via email (drugsafety@esperion.com) or via fax (+1-734-887-3988).

The Investigator is required to submit SAE reports to the IRB/IEC in accordance with local requirements. All Investigators involved in studies using the same investigational product will

receive any safety alert notifications for onward submission to their local IRB as required. All reports sent to Investigators will be blinded.

All SAEs should be recorded on the eCRF and source documents. Criteria for documenting the relationship to study drug and severity will be the same as those previously described.

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 and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the safety contact information provided on the SAE report form.

10.2.7.5. Reporting of Serious Adverse Events to Regulatory Authorities

The Sponsor (and/or designee) is responsible for submitting expedited reports of suspected and unexpected serious adverse reactions (SUSARS) to the appropriate regulatory authorities. All Investigators participating in ongoing clinical studies with the study drug will be notified by the Sponsor (or designee) of SUSARs. SUSARS must be communicated as soon as possible to the appropriate IRB/IEC by the investigator, as applicable and/or reported in accordance with local laws and regulations. Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

SAEs that are anticipated to occur in this patient population will be collected and reported by the Investigator as described in Section 10.2.7.4. However, these events will not be submitted to the regulatory authorities as expedited reports unless they meet SUSAR criteria. These events that are considered to be exempt from expedited reporting include the following clinical endpoints:

- CV death
- Nonfatal MI
- Nonfatal stroke
- Unstable angina requiring hospitalization
- Coronary revascularization
- Heart failure requiring hospitalization
- Noncoronary arterial revascularization

10.2.7.6. Reports of Pregnancy

If a patient becomes pregnant during the study or within 30 days of the last dose of study drug, the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor/SAE designee using the paper Pregnancy Report Form within the same timelines as an SAE.

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the paper Pregnancy Outcome Report Form should be completed and reported to the Sponsor.

Adverse events or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE CRF.

Patients who become pregnant will discontinue Investigational Medicinal Product (IMP) immediately and complete the end of study evaluations.

10.2.8. Reporting of Patient Death

The death of any patient during the study, or within the 30-day follow-up period after they have completed the study (regardless of the cause), must be reported as an SAE to the Sponsor/SAE designee

10.2.9. Recording of Adverse Events and Serious Adverse Events

Any AE that occurs following signing of the ICF through 30 days after completing the last study visit will be recorded on the AE eCRF.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

SAEs that occur during the study or within 30 days completing the last study visit, whether or not related to study drug, must be immediately reported to the Sponsor/SAE designee. The contact information for reporting of SAEs can be found on the SAE Reporting Form. After the 30-day reporting window, only SAEs assessed as related to study drug need to be reported.

10.2.10. Follow-Up of Adverse Events and Serious Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 30 days after the last dose of study drug. Any SAEs must be followed until resolution or stabilization, or until lost to follow-up. After the 30-day window, only treatment-related SAEs need to be reported.

10.2.11. Adverse Events of Special Interest (AESI)

[redacted]

10.2.11.1. Potential Adverse Events Based on Findings in Bempedoic Acid Clinical Studies

Across clinical studies to date, the most frequently reported TEAEs included musculoskeletal and connective tissue disorders (back pain, pain in extremity, myalgia, arthralgia, and muscle spasms), nervous system disorders (headache), gastrointestinal (GI) disorders (nausea and diarrhea), and infections and infestations. Overall, AEs were generally reported with similar incidence between those patients treated with bempedoic acid, bempedoic acid in combination with ezetimibe or statin therapy, ezetimibe, statins, or placebo; however, the incidence of headache was higher with bempedoic acid than placebo.

In general, laboratory results showed no clinically significant trends at the data cut-off for End-of Phase 2. A total of 7 patients receiving bempedoic acid monotherapy or in combination with a statin or ezetimibe experienced repeated and confirmed ALT and/or AST >3 × the ULN; in 1 of these patients receiving bempedoic acid 80 mg the elevation was assessed by Investigator as not related to study drug because the patient tested positive for acute cytomegalovirus (CMV) infection. One patient receiving ezetimibe monotherapy experienced repeated and confirmed ALT and/or AST >3 × ULN. All liver function test (LFT) abnormalities were considered mild to moderate and improved upon removal of the study drug. Small group mean increases in uric acid and homocysteine, and decreases in hemoglobin have been observed, but in general, these shifts have not been associated with clinical symptoms. Changes in vital signs, ECG, PE, and other physical findings presented no safety issues in any of the clinical studies.

Monitoring and Management of Elevated Serum Creatinine

If at any time after randomization, a patient experiences a decrease in eGFR to the level of 15 mL/min/1.73 m^2) or if the patient experiences acute renal failure, the patient should be withdrawn from IMP treatment but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3).

Monitoring and Management of Hemoglobin Change

If at any time after randomization a patient experiences a decrease >2.0 g/dL (20 g/L) from baseline (Week 0 [Visit T1]), the patient will undergo repeat confirmatory hematology testing as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat hematology assessment will include: 1) measurement of Hgb, hematocrit (Hct), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocyte count (percent and absolute), red blood cell count (RBC), and white blood cell count (WBC) with differential (absolute values only); 2) history of concomitant medication use; and 3) query for related symptoms. Additionally, further testing

may be warranted to rule out additional pathology depending on clinical presentation, and should be discussed with Esperion Therapeutics personnel or the authorized Medical Monitor.

- If repeat Hgb assessment confirms a decrease >2.0 g/dL (20 g/L) from baseline, the patient should be monitored carefully during the study and return at 2 week intervals after study completion for additional Hgb measurement until the level returns to baseline or reaches a stable level.
- If repeat Hgb assessment confirms Hgb <8 g/dL (80 g/L), the patient should be withdrawn from treatment with study drug. The patient will return at 1-week intervals after withdrawing from study drug treatment for additional Hgb measurement until the level returns to baseline or reaches a satisfactory conclusion.
- If the patient is withdrawn from study drug treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see Section 8.3).

At any time, the investigator may choose to consult with a specialist to further evaluate the cause of the alteration in hemoglobin.

10.2.11.2. Potential Adverse Events Based on Findings in Nonclinical Models

10.2.11.3. Adverse Events Associated with Other Lipid-Lowering Therapies

Adverse events that are currently monitored for all experimental lipid-lowering therapies and have been associated with previous lipid-lowering therapies and monitoring approach are listed below.

10.2.11.3.1. Cardiovascular Events

The occurrence of clinical endpoints (major adverse cardiovascular events) will be monitored and adjudicated by an independent blinded CEC throughout the bempedoic acid program. The details of the monitoring program can be found in the charter of the CEC. Standard monitoring will include occurrence of CV AEs, SAEs, including those as adjudicated by the CEC, standard vital signs, and ECGs.

10.2.11.3.2. Hepatic Function

Hepatic function will be monitored throughout with the clinical safety labs. More detailed investigation will occur if the safety clinical laboratory results are 3 times or more than the ULN).

If at any time after randomization a patient experiences a new ALT and/or AST >3 × ULN, the patient will undergo repeat confirmatory LFT assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat LFT assessment will include: 1) measurement of ALT, AST, alkaline phosphatase, total and direct bilirubin, prothrombin time (PT)/international normalized ratio (INR), eosinophil count, CK, antihepatitis A virus (total), HBsAg (confirmation of screening measurement), HCV (confirmation of screening measurement), and anti-cytomegalovirus/immunoglobulin M; 2) history of concomitant medication use; 3) history of exposure to environmental chemical agents, including ethanol; and 4) query for related symptoms. Additionally, further testing such as liver ultrasound or magnetic resonance imaging (MRI) scanning may be warranted to rule out additional pathology depending on clinical presentation and should be discussed with the Sponsor personnel or the authorized Medical Monitor.

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN, consideration should be given to withdrawing the patient and administering no further doses of study drug. At the investigator's discretion, study drug may be interrupted and the patient rechallenged with study drug after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >5 × ULN, patient should be withdrawn from study drug treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3) or more frequently if deemed appropriate by the Investigator.
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further treatment with study drug, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3) or more frequently if deemed appropriate by the Investigator:
  - TB >2 × ULN (will be fractionated if >2 × ULN and for those with Gilbert's Disease 2 × ULN conjugated (direct) bilirubin will be evaluated)
  - INR >1.5 × ULN (unless the patient is on stable dose of anticoagulation medication)

- Appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia

10.2.11.3.3. Muscle-Related Events

Muscle: Muscle events have been associated with statins and other lipid-lowering therapies and are mentioned in the product information for those products. The exact mechanism in the development of muscle events is unclear. Bempedoic acid is a prodrug which needs to be converted by an acyl-CoA synthetase (ACS) to a coenzyme A (CoA) ester (ETC-1002-CoA). The specific ACS known to convert bempedoic acid into its active form is not present in skeletal muscle. This suggests that bempedoic acid may not lead to an increase in muscular side effects when given in conjunction with statins. Nonetheless, muscle symptoms through AE review, CK elevations, and symptoms of potential myopathy will be closely monitored and will be recorded on eCRFs, including a muscle-specific AE eCRF. More detailed investigation will occur if laboratory CK results exceed 5 × ULN.

If at any time after randomization a patient experiences a marked CK elevation >5 × ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat CK assessment will include query for related symptoms.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic the patient should receive further assessment and investigation into the cause, assess whether there is renal injury and measure CK approximately weekly or more frequently if clinically indicated until resolution. If CK levels continue to rise; IMP should be discontinued.
- If symptomatic, the following should be completed:
  - Hold study drug
  - Clarification of the nature, duration, and intensity of muscle symptoms
  - Review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology)
  - Evaluation for additional diagnoses or other conditions which can cause myopathy including muscle tenderness (by PE), weakness, rash, measurement of serum creatinine, dipstick urinalysis with microscopy if indicated
  - Obtain clinical chemistries to assess the possibility of lactic acidosis
  - Follow symptoms and CK until the abnormality has resolved
  - If based on the above evaluation an alternative explanation is suspected, consideration can be given to resuming study drug once CK returns to baseline levels
  - If no alternative explanation exists, consideration should be given to withdrawing the patient from study drug treatment.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality as listed below, the patient should be withdrawn and given no further doses of study drug:
  - >10 × ULN, even in the absence of symptoms. For CK elevations >10 × ULN, hold study drug treatment until the repeat value returns, is evaluated, and is <10 × ULN before restarting study medication.
  - In all cases, evaluate the signs/symptoms and laboratory evaluations as outlined above.
- If the patient is withdrawn from study drug treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see Section 8.3).

10.2.11.3.4. Diabetes and Hyperglycemia

Diabetes and Hyperglycemia: New onset diabetes has been associated with the use of statins and is dose related. The product information for statins mentions hyperglycemia increased HbA_{1C} and increases in fasting glucose as potential adverse reactions. Hyperglycemia occurred in 10.8% (n = 10) of the placebo treated patients vs none of the bempedoic acid 180 mg treated patients in the Phase 2 program. Regardless, new onset diabetes through AE monitoring will be captured and summarized for this study and across all of the bempedoic acid studies. Clinical safety laboratories will also be evaluated during the studies including HbA_{1C}, and fasting glucose.

10.2.11.3.5. Renal

Nonclinical studies have demonstrated nephrotoxic effects on tubular cells of some lipid-modifying agents. In the Phase 2 program, creatinine elevations >25% over baseline occurred in 1 subject in the bempedoic acid 80 mg, 2 in the 180 mg, 1 in the 180 mg + ezetimibe, 1 in the 240 mg, and 3 in the 240 mg + baseline statin. In most cases, this elevation occurred at the end of the study and the values were not repeated and the events were not considered related. In 1 case, repeat values were obtained and the subject's creatinine was returning to baseline by Week 12. None exceeded a serum creatinine >1.8 mg/dL. No subjects withdrew due an AE of increased creatinine. Patients will be monitored beyond the conclusion of the study if necessary to follow abnormal renal laboratory values until resolution or stabilization.

If at any time after randomization, a patient experiences a decrease in eGFR to the level of 15 mL/min/1.73 m^2) or if the patient experiences acute renal failure, the patient should be withdrawn from study drug treatment but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3)

10.2.11.3.6. Neurocognitive Events

Theoretically, it is possible that lipid-lowering agents that disrupt cholesterol homeostasis in the brain could impact neurological function, and there have been reports of cognitive impairment (eg, memory loss) associated with the use of statin drugs (Food and Drug Administration 2012). The human brain has a significant requirement for cholesterol (Dietschy 2001; Dietschy 2004)

and dysregulation of brain cholesterol homeostasis has been linked to chronic neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, Niemann–Pick type C disease and Smith-Lemli-Opitz syndrome (Goedeke 2014). In the Phase 2 program, the only disorder in this system organ class (SOC) that occurred more commonly in the bempedoic acid treated group was headache. For the ongoing program, neurocognitive events will be evaluated by standard PE and adverse monitoring. Summarization of events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms.

10.2.12. Monitoring and Management of Elevated Triglycerides

Patients may continue to use stable doses of TG-lowering medications during the study. An adjunctive therapy plan is in place for those patients whose TG values meet the protocol-defined threshold criteria. Post-randomization, TG results will be masked to investigators in order to maintain the blind; however, a threshold has been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen. Beginning at Week 4 (Visit T2), if the TG level exceeds >1000 mg/dL (11.3 mmol/L) while on treatment, the investigator will receive notification from the central laboratory that the patient has met or exceeded the protocol-defined threshold criteria for TG. The investigator will initiate the following plan:

- Any patient with TG >1000 mg/dL (11.3 mmol/L), will be reminded to fast for at least 10 hours and will return to clinic within 1 week for a repeat, fasting TG sample to confirm the TG value meets the threshold criteria
- Any patient with a confirmed TG >1000 mg/dL (11.3 mmol/L) may initiate standard-of-care therapy to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.
- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from study drug treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3).
- Please see the Clinical Laboratory Manual for sample collection and instructions.

10.3. Data Monitoring Committee (DMC)

An independent DMC will monitor unblinded accumulating patient safety and efficacy data until the last patient has completed study treatment. In addition, data on SAEs and deaths, including clinical endpoints, will be monitored by the DMC during this period. At each DMC review, relevant unblinded safety and efficacy information from ongoing studies of bempedoic acid will be provided to the DMC by an independent unblinded statistician and programmer. Additional details will be provided in a DMC Charter.

10.4. Clinical Event Committee (CEC)

A blinded independent expert CEC will adjudicate clinical endpoints including all MACE and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal MI

(MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet SAE criteria will be reported as SAEs. Additional details regarding clinical endpoints and clinical endpoint definitions are outlined below and will be included in the CEC charter. The charter will also outline the committee's composition, meeting timelines, and members' roles and responsibilities. Clinical endpoints from this study and other studies within the bempedoic acid Phase 3 development program will be aggregated to allow for a safety assessment across the entire development program.

11. STATISTICS

11.1. General Considerations

The statistical analyses described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP). The SAP will supersede the protocol in the event of any differences between the 2 documents in relation to data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

11.2. Sample Size

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C.

11.3. Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy analyses, is defined as all randomized patients. The FAS is also known as the intention-to-treat (ITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received.

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of study medication. Patients in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

11.4. Disposition, Demographics and Baseline Characteristics

Disposition, including reason for withdrawal from the study, will be summarized by treatment group. Demographic information and patient characteristics including, but not limited to, gender, race, age, and baseline vital signs will also be summarized by treatment group.

11.5. Primary Endpoint Analysis

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. Baseline is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1).

The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group and patient type (primary prevention; secondary prevention) as factors and

baseline LDL-C as a covariate. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. The details of the ANCOVA model and options to account for unequal variances and group size will be described in the SAP.

Missing data for the primary endpoint will be imputed using a multiple imputation method that accounts for treatment adherence. A pattern mixture model (PMM) will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Patients with missing LDL-C data at Week 12 who are no longer taking study treatment can be assumed no longer to be benefitting from study medication, and their missing value(s) can be assumed to be similar to those from placebo patients. In this instance, it is reasonable to impute LDL-C values in a model including placebo patients' data only. Patients with missing LDL-C data at Week 12 who are still taking study treatment can be assumed to continue to benefit from study medication, and their missing value(s) can be assumed to be similar to those who remain on study treatment and have data. In this instance, it is reasonable to impute LDL-C values based on the observed values in their randomized treatment group at Week 12. Details for the PMM will be described in the SAP.

To account for uncertainty, missing values will be imputed using multiple imputation. Imputed datasets will be analyzed using an ANCOVA model with the treatment and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. Approximately 200 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

11.6. Secondary and Tertiary Endpoint Analysis

Secondary efficacy endpoints are also of interest for this study, in terms of controlling the overall Type I error rate, a gatekeeping or stepdown approach will be used to test the primary efficacy endpoint and then specific secondary efficacy endpoints sequentially in order to preserve the study-wise Type I error rate. The sequence for the stepdown procedure in this study is as follows:

1. Test the primary efficacy endpoint: percent change from baseline to Week 12 in LDL-C
2. Test the percent change from baseline to Week 24 in LDL-C
3. Test the percent change from baseline to Week 12 in non-HDL-C
4. Test the percent change from baseline to Week 12 in TC
5. Test the percent change from baseline to Week 12 in apoB
6. Test the percent change from baseline to Week 12 in hs-CRP

In this hierarchical testing structure, each hypothesis is tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. If the primary endpoint meets the criteria for statistical significance, then the percent change from baseline to Week 24 in LDL-C will be tested; and so forth.

For the remaining secondary efficacy endpoints and the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints, the p-values for those endpoints will be considered descriptive.

In general, change or percent change in lipid parameters at a given time point will be analyzed using similar ANCOVA model for the primary endpoint with treatment group and patient type (primary prevention; secondary prevention) as factors and the relevant baseline as a covariate.

Baseline for [redacted] non-HDL-C, [redacted] and TC is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value.

Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Same imputation method described for the primary endpoint will be used for those secondary endpoints included in the step-down procedure, while only observed data analysis will be used for other secondary and tertiary endpoints. For each lipid parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

The ANCOVA assumption of normality will be assessed. If severe non-normality of the data is found at any time point for any parameter, either the data will be transformed so that it is normally distributed or a nonparametric test will be considered instead of the planned ANCOVA.

Finally, the number and percent of patients in each treatment group requiring additional (post-randomization) TG-lowering therapy will be summarized. The medications will be summarized by treatment group.

11.7. Safety Analysis

The summarization of AEs will include TEAEs, defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not related to the product. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. These AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, coagulation, HbA_{1C}, glucose, and urinalysis; PE findings; vital signs; ECG readings; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each post baseline time point.

Hepatic Safety

For liver-associated enzymes and TB, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. Hy's law criteria (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN (conjugated [direct] if Gilbert's Disease) in the absence

of other known causes) will also be applied to the data; any potential Hy's law cases will be listed separately.

Musculoskeletal Safety

AEs of muscle-related symptoms will be summarized by treatment group. In addition, the number and percent of patients with abnormal CK values will be summarized.

Diabetes/Glycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group.

Renal Safety

Baseline eGFR and values of CK will be summarized by treatment group and by baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using prespecified MedDRA terms and will be performed by treatment group.

Clinical endpoints

Clinical endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the bempedoic acid program. Adjudicated clinical endpoints will be summarized by event type and treatment group. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

11.8. Pharmacokinetics

Three plasma PK samples for analysis will be collected. Plasma concentrations of bempedoic acid and optionally, one or more of its metabolites, will be determined in patients who are receiving bempedoic acid. All patients, site personnel, and study personnel will remain blinded to treatment assignment throughout the duration of the study. Personnel performing the bioanalytical analysis of bempedoic acid concentrations will be unblinded in order to assay the appropriate samples during the study. Plasma concentrations of bempedoic acid and any measured metabolite will be included in the listings, but population PK analysis will be reported separately will be descriptive by time point.

11.9. Interim Analysis and Data Monitoring Committee

There are no planned interim analyses for this study. An independent DMC will review accumulating unblinded safety data from this study and other ongoing studies of bempedoic acid. Additional details regarding the DMC will be included in the DMC Charter.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation (ICH) and GCP guidelines, national and international regulatory requirements, and the current Declaration of Helsinki throughout its duration by means of personal visits to the Investigator's facilities and other communications.

These visits will be conducted to evaluate the progress of the study, verify the rights and well-being of the patients are protected, and verify the reported clinical study data are accurate, complete, and verifiable from source documents. This includes review of ICDs, results of tests performed as a requirement for participation in this study, and any other medical records (eg, laboratory reports, clinic notes, study drug dispensing log, pharmacy records, patient sign-in sheets, patient-completed questionnaires, telephone logs, ECGs) required to confirm information contained in the eCRFs.

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA and European Medicines Agency (EMA) recommendations, and will be described in details by the study-specific risk-based monitoring plan.

A monitoring visit should include a review of the essential clinical study documents (regulatory documents, case report forms, medical records and source documents, drug disposition records, patient informed consent forms, etc) as well as discussion on the conduct of the study with the Investigator and staff.

The monitor should conduct these visits as frequently as appropriate for the clinical study. The Investigator and staff should be available during these visits for discussion of the conduct of the study as well as to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

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

12.2. Audits and Inspections

Representatives of the Sponsor or its authorized clinical quality assurance group may visit a clinical site at any time during the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must be respected. The Investigator and clinical site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its authorized representative.

The clinical study may also be inspected by the FDA or EMA (or other regulatory authority) to verify that the study was conducted in accordance with protocol requirements, as well as the applicable regulations and guidelines.

In the event the Investigator is contacted by regulatory authorities who wish to conduct an inspection of the clinical site, the Investigator will promptly notify the Sponsor of all such requests and will promptly forward a copy of all such inspection reports.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor/ designee may conduct a quality assurance audit. Please see Section 12.2 for more details regarding the audit process.

14. ETHICS

14.1. Institutional Review Board/Independent Ethics Committee Approval

Before initiation of the study, the Investigator must obtain approval or favorable opinion of the research protocol, ICD, and any material related to patient recruitment from an IRB or IEC. For locations participating within the US, the IRB must comply with the provisions specified in 21 CFR Part 56, ICH and GCP guidelines, and applicable pertinent state and federal requirements. For locations participating outside of the US, the IRB or IEC must comply with the applicable requirements of each participating location, including ICH and GCP guidelines, except where a waiver is applicable

IRBs and IECs must be constituted according to the applicable laws. It is the responsibility of each clinical site to submit the protocol, IB, patient informed consent, patient recruitment materials (if applicable), and other documentation as required by the IRB or IEC for review and approval. A copy of the written approval must be provided to the Sponsor.

The documentation should clearly mention the approval/favorable opinion of the protocol, the patient informed consent form, and patient recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRBs or IECs and provided to the Sponsor prior to the release of clinical study supplies to the clinical site and commencement of the study. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

Clinical sites must adhere to all requirements stipulated by their respective IRB or IEC. This includes notification to the IRB or IEC regarding: protocol amendments, updates to the ICD, recruitment materials intended for viewing by patients, aggregate safety reports required by regulatory competent authorities, serious and unexpected AEs, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of final study reports and summaries to the IRB or IEC.

It is the responsibility of each clinical site to submit information to the appropriate IRB or EC for annual review and annual re-approval.

The Investigator must promptly inform their IRB or IEC of all SAEs or other safety information reported from the patient or the Sponsor.

14.2. Ethical Conduct of the Study

The investigator agrees, when signing the protocol, to conduct the study in accordance with ethical principles that have their origin in the current revision of the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and policies and procedures as outlined by the ethical requirements for IRB or IEC review and ICDs.

The Investigator agrees to allow monitoring and auditing of all essential clinical study documents by the Sponsor or its authorized representatives and inspection by the FDA, EMA, or other appropriate regulatory authorities. Monitoring and auditing visits by the Sponsor or

authorized designee will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The Investigator will assure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperates with monitoring and audits, and will demonstrate due diligence in recruiting and screening study patients. The Investigator must sign and return to the Sponsor the "Investigator's Signature" page (see Appendix 3) and provide a copy of current curriculum vitae. For this study and all studies conducted under an Investigational New Drug (IND) application, the Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to the Sponsor (or designee). For European Union (EU) investigators, equivalent information contained within the FDA 1572 form may be requested unless a waiver has been requested and received by the Sponsor from the FDA.

14.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time, but will be encouraged to continue in the study for safety follow-up (see Section 8.4). The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICD. A copy of the signed ICD must be given to the patient.

14.4. Patient Confidentiality

The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor (or the Sponsor's authorized representative). If a patient's name appears on any document, it must be redacted and replaced with the patient identifier before a copy of the document is supplied to the Sponsor or Sponsor's authorized representative. The ICD must include appropriate statements explaining that patient data will be confidential and what actions will be taken to ensure patient confidentiality.

Any other confidentiality requirements specified by the site, IRB or IEC, or national or local regulations will be adhered to and detailed appropriately in the ICD.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

Applicable regulations require the Sponsor (or the Sponsor's authorized representative) to inspect all documents and records to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) for the patients in this study. These regulations also allow the Sponsor's records to be inspected by authorized representatives of the regulatory agencies. The Investigator will permit study-related monitoring, audits, IRB or IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

15.2. Retention of Records

In compliance with the ICH/GCP guidelines, the Investigator/Institution agrees to retain and maintain all study records that support the data collected from each patient, as well as all study documents as specified in ICH/GCP, Section 8 Essential Documents for the Conduct of a Clinical Trial. The Investigator agrees to contact the Sponsor before destroying or relocating any study documentation and is expected to take measures to prevent accidental or premature destruction of these documents.

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be contacted in writing regarding the name and address of the new person responsible as well as the disposition of document storage. Under no circumstances shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

Essential records (including eCRFs, source documents, study drug disposition records, signed patient ICDs, AE reports, and other regulatory documents) as required by the applicable regulations, must be maintained for 2 years after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the investigational product.

It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

15.3. Case Report Forms and Study Records

Access to eCRFs will be provided to the clinical site. As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (eg, IRB or IEC correspondence, clinical study materials and supplies shipment

manifests, monitoring logs, and correspondence). A study-specific binder will be provided with instructions for the maintenance of study records.

Source documentation is defined as any hand-written or computer-generated document that contains medical information or test results that have been collected for or in support of the protocol specifications (eg, laboratory reports, clinic notes, study drug disposition log, pharmacy records, patient sign-in sheets, patient completed questionnaires, telephone logs, x-rays, and ECGs). All draft, preliminary, and pre/final iterations of a final report are also considered to be source documents (eg, faxed and hard copy of laboratory reports, faxed and hard copy of initial results, and final report).

The Investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by the Sponsor or its authorized representatives and inspection by the appropriate regulatory authorities.

Data reflecting the patient's participation with the study drug under investigation are to be reported to the Sponsor. The data are to be recorded on the eCRFs and/or other media provided or approved by the Sponsor.

A completed eCRF must be submitted for each patient who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality. The eCRF should not be used as a source document unless otherwise specified by the Sponsor.

Neither the Sponsor nor a service provider contracted to analyze data and complete the study report is permitted to interpret a blank answer; therefore, all fields should be completed. All requested information must be entered on the eCRFs. If an item is not available or is not applicable, this fact should be indicated as not available (N/A) or not done (N/D); do not leave a field blank.

Each set of completed eCRFs must be signed and dated by the Investigator acknowledging review and that the data are accurate and complete. The completed database is to be returned to the Sponsor as soon as practical after completion by the mechanism prescribed for the protocol.

It is essential that all dates appearing on the Sponsor's patient data collection forms for laboratory tests, cultures, etc, be the dates on which the specimens were obtained or the procedures performed. The eCRFs will be electronically signed by the Investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed within a timely manner according to the CRF completion guidelines.

16. ADMINISTRATIVE CONSIDERATIONS

16.1. Investigators

The Investigator must agree to the responsibilities and obligations listed below, as specified by the appropriate FDA/EMA regulatory requirements or ICH/GCP guidelines:

- Agree to conduct the study in accordance with the relevant current protocol
- Agree to personally conduct or supervise the described investigation(s)
- Agree to inform any patients, or persons used as controls, that the study drugs are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval are met
- Agree to report adverse experiences that occur during the course of the investigation(s)
- Read and understand the information in the IB, including the potential risks and side effects of the study drug
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments
- Maintain adequate and accurate records and make those records available for inspection
- Ensure that an appropriate IRB/IEC will be responsible for the initial and continuing review and approval of the clinical investigation
- Agree to promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to patients or others
- Agree to not make changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to patients
- Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements.
- Refer also to:
- FDA Regulations Related to GCP and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
- Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html
- Guidance for IRBs and Clinical Investigators: http://www.fda.gov/oc/ohrt/irbs/default.htm
- DIRECTIVE 2001/20/EC: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

- Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf

16.2. Study Administrative Structure

Investigational medicinal product supply chain details can be found in the pharmacy manual.

Central Laboratory:

Bioanalytical Laboratory:

Randomization, IWRS, Statistical Analysis, Study Management and Monitoring, Data Management, Medical and Safety Services including Medical Monitoring (see Medical and Safety Services below), Programming, and Medical Writing:

Medical and Safety Services:

Global Medical Monitor

16.3. Amendments

Changes to the research covered by this protocol must be implemented by formal protocol amendment. All amendments to the protocol must be initiated by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IRB or IEC approval. Documentation of amendment approval by the Investigator and IRB or IEC must be provided to the Sponsor or its authorized representative. When the change(s) involve only logistic or administrative aspects of the study, the IRB or IEC only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the Investigator will contact the Medical Monitor. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Medical Monitor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded on the eCRF and source documents will reflect any departure from the protocol and the source documents will describe the departure and the circumstances requiring it.

16.4. Financial Disclosure

Prior to the start of the study, Investigators will release sufficient and accurate financial information that permits the Sponsor to demonstrate that an Investigator and all study relevant assigned personnel have no personal or professional financial incentive regarding the future approval or disapproval of the study drug such that his or her research might be biased by such incentive.

17. PUBLICATION AND DISCLOSURE POLICY

It is understood by the Investigator that the information and data included in this protocol may be disclosed to and used by the Investigator's staff and associates as may be necessary to conduct this clinical study.

All information derived from this clinical study will be used by the Sponsor (or designee) and therefore, may be disclosed by the Sponsor (or designee) as required to other clinical Investigators, to the FDA, EMA, and to other government agencies, or in connection with intellectual property filings or publications. In order to allow for the use of the information derived from this clinical study, it is understood by the Investigator that there is an obligation to provide the Sponsor with complete test results and all data from this clinical study. The Investigator agrees to maintain this information in confidence, to use the information only to conduct the study, and to use the information for no other purpose without the Sponsor's prior written consent (or as otherwise may be permitted pursuant to a written agreement with the Sponsor or its designee).

The results of the study will be reported in a clinical study report prepared by the Sponsor (or designee), which will contain eCRF data from all clinical sites that conducted the study.

The Sponsor shall have the right to publish data from the study without approval from the Investigator. Manuscript(s) and abstract(s) may only be prepared through cooperation between the Sponsor (or designee) and the study Investigator(s). If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review in accordance with the provisions of such Investigator's written agreement with the Sponsor (or designee) before submission for publication or presentation. If requested by the Sponsor in writing, the Investigator will withhold such publication in accordance with the provisions of such agreement.

18. REFERENCES

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World Health Organization (WHO) Fact Sheet No 317 Updated January 2015.

19. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -35±7**	**Day -28±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
Statin Intolerance Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight[4]	X			X			X	X
Height/BMI	X							
12-Lead ECG[5]			X					X
Vital Signs[6]	X	X	X	X	X		X	X
Serology[7]	X							
Serum Pregnancy/FSH[8]	X							
Urine Pregnancy[9]				X				
TSH	X							
Clinical Safety Labs[10]	X		X	X	X		X	X
Basic Fasting Lipids[11]	X		X	X	X		X	X
HbA_{1C}	X			X			X	X
PK Sample					X		X	X
apoB				X			X	X
hs-CRP				X			X	X
Diet and exercise counseling[12]	X	X	X	X	X	X	X	
Establish Patient Eligibility		X		X				
Randomization				X				
IWRS Contact[13]	X	X		X			X	X
Single-blind Drug Dispensing		X						
Double-blind Drug Dispensing				X			X	
Drug Return/Compliance			X	X	X		X	X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visits, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs).

[1] An optional fasting (minimum of 10 hours) TG assessment MAY be completed between Visit S1 and Visit S2 (prior to starting single-blind medication) if patient fails to meet TG entry criterion at Visit S1. If this optional TG is completed, the repeat value will be used to determine eligibility.

[2] A recheck of blood pressure may be completed between Visits S1 and S2 if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (diastolic blood pressure [DBP] and/or systolic blood pressure [SBP]) do not meet exclusionary values. Repeat labs may be completed at Visit S2 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

[4] Body weight will be measured while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[5] Single 12-lead ECG will be performed prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

[7] Serology for HBsAg, HCV-ABVivi.

[8] Pregnancy test completed in women of child-bearing potential only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

[9] Urine pregnancy test completed in women of child-bearing potential only just prior to randomization.

[10] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. A coagulation panel will be completed for all patients at Week -5 (Visit S1). A coagulation panel will be completed only for patients on anti-coagulant therapy at Day 1 (Visit T1) and 3 to 5 days later. For these visits, the sample may be analyzed at either the central or a local lab. Please refer to laboratory manual for detailed schedule of tests.

[11] Basic fasting (minimum of 10 hours) lipids include total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides.

[12] Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

[13] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

APPENDIX 2. SPONSOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant

Study Number: 1002-046

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: 17 Apr 2017

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant

Study Number: 1002-046

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: 17 April 2017

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant

Study Number: 1002-046

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: 4/17/2017

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant

Study Number: 1002-046

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: 4/17/17

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed: _____ Date: _____

Name and Credentials:
Title:
Affiliation:
Address:
Phone Number:

APPENDIX 4. STATIN INTOLERANCE CONFIRMATION FORM

Patient Identification (Please Print or Type)

Name: _____

Initials: _____

Screening Number: _____

Patient

My doctor has recommended that I take a medication (called a statin) to reduce the bad cholesterol (fats) in my blood. My doctor has told me that a statin would reduce my risk of a heart attack or stroke and the risk of death. However, I am not taking a statin (or I am taking a statin only at a very low dose) because of side effects. These side effects began or became worse when I was taking the statin and then went away or improved when I stopped taking it or decreased the dose. I can't tolerate these medications (called statins) even though I know they would reduce my risk of a heart attack or stroke or death.
Date **Signature of Patient**

Principal Investigator

For the purposes of the 1002-046 clinical study, in my opinion, this patient is unable to tolerate statin therapy (except possibly at very low average daily doses of atorvastatin <10 mg, fluvastatin <40 mg, lovastatin <20 mg, pravastatin <40 mg, pitavastatin <2 mg, rosuvastatin <5 mg or simvastatin <10 mg) based on my review of the medical and medication histories and discussion with the patient.
Date **Signature of Principal Investigator**

APPENDIX 5. DUTCH LIPID CLINIC NETWORK CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia[1,2,3]

Diagnostic Scoring for Familial Hypercholesterolemia	
CRITERIA	POINTS POSSIBLE
Family History	
First-degree relative with known premature[a] coronary and vascular disease, *OR* First-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, *OR* Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical History	
Patient with premature[a] coronary artery disease	2
Patient with premature[a] cerebral or peripheral artery disease	1
Physical Examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol Levels mg/dL (mmol/L)	
LDL-C ≥330 mg/dL (≥8.5 mmol/L)	8
LDL-C 250-329 mg/dL (6.5-8.4 mmol/L)	5
LDL-C 190-249 mg/dL (5.0-6.4 mmol/L)	3
LDL-C 155-189 mg/dL (4.0-4.9 mmol/L)	1
DNA Analysis	
Functional mutation in the LDLR, apoB, or PCSK9 gene	8

apoB = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; FH = familial hypercholesterolemia; PCSK9 = Proprotein convertase subtilisin/kexin type 9.

[a] Premature ≤55 years in men; ≤60 years in women

Scoring:

Diagnosis (Diagnosis Based Upon Total Score Obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6-8
Possible Familial Hypercholesterolemia	3-5
Unlikely Familial Hypercholesterolemia	<3

References:

1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160:407-20.
2. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012;23:282-9.
3. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:2478-3490a.

APPENDIX 6. SIMON BROOM REGISTER DIAGNOSTIC CRITERIA FOR HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia[1]

Definite Familial Hypercholesterolemia:

- Required laboratory = high cholesterol levels:
  - Adult = Total cholesterol levels >290 mg/dL (7.5 mmol/L) or LDL-C >190 mg/dL (4.9 mmol/L)
  - Child less than 16 years of age = Total cholesterol levels >260 mg/dL (6.7 mmol/L) or LDL-C >155 mg/dL (4.0 mmol/L)
- Plus at least one of the two:
  - Plus physical finding = tend xanthomas, or tendon xanthomas in first or second degree relative

  OR

  - DNA-based evidence of an LDL-receptor mutation, familial defective apoB-100, or PCSK9 mutation

Possible Familial Hypercholesterolemia:

- Required laboratory = high cholesterol levels:
  - Adult = Total cholesterol levels >290 mg/dL (7.5 mmol/L) or LDL-C >190 mg/dL (4.9 mmol/L)
  - Child less than 16 years of age = Total cholesterol levels >260 mg/dL (6.7 mmol/L) or LDL-C >155 mg/dL (4.0 mmol/L)
- Plus at least one of the two:
  - Family history of myocardial infarction at:
    - Age 60 years or younger in first degree relative
    - Age 50 years or younger in second degree relative

  OR

  - Family history of elevated total cholesterol
    - Greater than 290 mg/dL (7.5 mmol/L) in adult first or second degree relative
    - Greater than 260 mg/dL (6.7 mmol/L) in child, brother or sister aged younger than 16 years

References:

1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160:407-20.

APPENDIX 7. SUMMARY OF CHANGES AMENDMENT 1

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-046
Study Title:	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C Who are Statin Intolerant
Protocol Version Incorporating Current Summary of Changes:	Amendment 1: 10 April 2017
Preceding Protocol Version:	Original Protocol: 25 August 2016
Investigational Product Name:	ETC-1002

Conventions used in this Summary of Changes Document

1. The text immediately preceding and following a change to the protocol is included for each change in order to provide the reviewer with a reference point to identify the change in the protocol.
2. All locations (ie, section numbers and/or header text) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.
3. The original text is from the preceding protocol version.
4. In the "New Text", all substantive text added to the protocol is bolded and italicized.
5. In the "New Text", text deleted from the protocol is indicated in strikethrough font.

Summary and Justification of Changes

The protocol was amended for the following:

- Updated Sponsor details on the title page and in the Sponsor signature section
- Added a line for Amendment 1 version and date to reflect amendment version details.
- Revised secondary and tertiary endpoints as well as added safety endpoints to more accurately describe statistical testing and analysis.

- Under inclusion criteria
  - Added topical method to allowable forms of hormonal contraception.
  - Added requirement that women use 2 rather than 1 form of acceptable contraception based on a request from the European Heads of Medicines Agency's Voluntary Harmonization Procedure review of another Esperion sponsored protocol. In addition, specified the period that contraception should be followed. This amendment is to maintain consistency across protocols and is not based on any new data with bempedoic acid.
  - Added expanded definition of 'true abstinence.
  - Added an additional fasting LDL-C assessment (Week -1 (Visit S3) ≥70 mg/dL (1.8 mmol/L) after the Run-in period to inclusion criteria. Removed the allowance of repeating a screening LDL-C measurement after Visit S1.
  - Clarified the timing of the collection of lipid values with reference to PCSK9 inhibitor injections in order to ensure lipid values are obtained at trough levels of PCSK9.
- Under exclusion criteria
  - Revised exclusionary blood pressure to systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg based on a request by Health Canada. Instructions regarding repeat measures of blood pressure were further clarified.
  - Shortened the window that obesity medications should not be initiated or changed before randomization from 3 months to 4 weeks.
  - Clarified language around PCSK9 inhibitor use prior to screening.
  - Added an exclusion for women who are pregnant, breastfeeding or intending to become pregnant within 30 days after the last dose of study drug.
  - Based on the extremely long half-lives of experimental siRNA inhibitors, eg, Inclisiran, excluded patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9.
  - Excluded gemfibrozil in patients taking very low dose statins per the co-administration prescribing instructions.
- Removed collection of optional genetic sampling.
- Removed collection of reserve samples.
- Removed collection of pharmacokinetic (PK) sample collection on Day 1 and clarified that collection needs to be prior to dosing at visits where PK samples are collected.
- Updated text pertaining to bempedoic acid mechanism of action based on new information.

- Removed manufacturing contact details from the protocol and indicated the details will be described in the pharmacy manual.
- Updated the sections on prohibited and allowed medications to reflect the following:
  - Added inhaled steroids to allowable stable systemic corticosteroids at screening.
  - Noted that fibrates could not be used within 6 weeks prior to screening versus within 4 weeks for other hypertriglyceridemia medications.
- Specified that documentation for the name of two statins and dose of at least one statin attempted at a low dose is required.
- Added a section on overdose management based on a request from Health Canada.
- Based on a request from the FDA, the monitoring and management of CK values for asymptomatic patients was modified.
- Updated text around reporting of Adverse Events and Pregnancies.
- Added the following sections to the protocol:

  Definition of Serious Adverse Event Events or Outcomes not qualifying as Serious Adverse Events

  Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events
- Revised statistical sections regarding
  - methods for imputation of missing data for primary, secondary, and tertiary endpoints.
  - how ANCOVA model will be applied to primary, secondary, and tertiary endpoints.
- Made administrative changes throughout the protocol where required to correct inconsistencies, add clarification, or correct errors.

CHANGE 1 REVISION OF TITLE PAGE INFORMATION

Location:

Title Page

Original Text:

Sponsor Contact: [redacted]

Version	Date
Original Protocol:	25 August 2016

New Text:

Sponsor Contact: [redacted]

Version	Date
Original Protocol:	25 August 2016
Amendment 1:	***10 April 2017***

CHANGE 2 MECHANISM OF ACTION REVISION

Location:

Section 4.2.1, Mechanism of Action

Original Text:

An important differentiating feature of bempedoic acid is that it does not inhibit cholesterol synthesis in skeletal muscle. In addition to preliminary data suggesting that only minor amounts of bempedoic acid enters skeletal muscle (<5% of systemic exposure), skeletal muscle does not express the enzyme required to activate bempedoic acid to ETC-1002-CoA and inhibit ACL. Therefore, bempedoic acid is not anticipated to mediate the adverse effects associated with inhibition of biological intermediates within the cholesterol biosynthesis pathway in skeletal muscle.

New Text:

An important differentiating feature of bempedoic acid is that, ***unlike statins,*** it does not inhibit cholesterol synthesis in skeletal muscle. ***The enzyme required to convert bempedoic acid to ETC-1002-CoA is not present in skeletal muscle***~~. In addition to preliminary data suggesting that only minor amounts of bempedoic acid enters skeletal muscle (<5% of systemic exposure), skeletal muscle does not express the enzyme required to activate bempedoic acid to ETC-1002-~~

~~CoA and inhibit ACL.~~ Therefore, bempedoic acid is not anticipated to mediate the adverse effects associated with inhibition of biological intermediates within the cholesterol biosynthesis pathway in skeletal muscle***; however, the safety of bempedoic acid and its metabolites regarding human skeletal muscle is not yet established.***

CHANGE 3 EFFICACY AND SAFETY ENDPOINT REVISIONS

Location:

Section 2, Synopsis; Section 5.2, Study Endpoints

Original Text:

5.2.1. Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C

5.2.2 Secondary Endpoints

1. Percent change from baseline to Week 24 in LDL-C
2. Change from baseline to Weeks 12 and 24 in LDL-C
3. Percent change from baseline to Week 12 in non-HDL-C, TC, apoB, and hs-CRP

5.2.3. Tertiary Endpoints

[redacted]

New Text:

5.2.1. Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C

5.2.2 Secondary Endpoints

1. Percent change from baseline to Week 24 in LDL-C
2. ~~Change from baseline to Weeks 12 and 24 in LDL-C~~Percent change from baseline to Week 12 in non-HDL-C, TC, apoB, and hs-CRP
3. ***Absolute change from baseline to Weeks 12 and 24 in LDL-C***

5.2.3. Tertiary Endpoints

[redacted]

5.2.4 Safety Endpoints

1. ***Patient incidence to TEAE***
2. ***Safety laboratory values and vital signs***
3. ***Cardiovascular event rates***

CHANGE 4 STUDY METHODOLOGY REVISIONS

Location:

Section 2, Synopsis; Section 6.2, Study Population and Selection

Original Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 71 clinical sites in North America. Screening Week -5 (Visit S1) will be approximately 5 weeks prior to randomization but can be extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons. Eligible patients will return to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo study drug. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel regarding their eligibility status and considered screen failures. As necessary, for reasons of safety if a patient begins the run-in period but screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of AEs.

New Text:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 71 clinical sites in North America. Screening Week -5 (Visit S1) will be approximately 5 weeks prior to randomization. ***The time period between Visits S1 and S2***~~but can be~~ extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons. Eligible patients will return to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo study drug. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel regarding their eligibility status and considered screen failures. As necessary, for reasons of safety if a patient begins the run-in period but screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of AEs.

CHANGE 5 SUBJECT INCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis; Section 6.2.1, Subject Inclusion Criteria

Original Text:

2. Men and nonpregnant, nonlactating women. Women must be either:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      – ≥55 years, **or**
      – <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; or
   c. Women of childbearing potential willing to use 1 acceptable method of birth control including:
      – oral, implanted, or injectable birth control medications
      – placement of an intrauterine device with or without hormones
      – barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
      – vasectomized male partner who is the sole partner for this patient
      – true abstinence (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal)

   There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
3. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -5 (Visit S1)
4. Fasting (minimum of 10 hours) calculated LDL-C at Week -5 (Visit S1)
   - Primary prevention ≥130 mg/dL (3.4 mmol/L)
   - Secondary prevention and/or heterozygous familial hypercholesterolemia (HeFH) ≥100 mg/dL (2.6 mmol/L)

   Note: A single repeat of LDL-C may be completed prior to initiation of the single-blind Run–in period. For those patients who have a repeat LDL-C, the mean of the first value and the repeat value will be used to determine eligibility.

   For patients taking proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (eg, alirocumab and evolocumab), doses must be administered on a consistent schedule and the study lipid values must be obtained within 24-48 hours prior to the next planned dose of the PCSK9 inhibitor.

New Text:

2. Men and nonpregnant, nonlactating women. Women must be either:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      – ≥55 years, **or**
      – <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; or
   c. Women of childbearing potential ***must be*** willing to use ~~1~~ ***2*** acceptable method***s*** of birth control ~~including~~ ***(unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include***:
      – oral, implanted, ***topical,*** or injectable birth control medications
      – placement of an intrauterine device with or without hormones
      – barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
      – vasectomized male partner who is the sole partner for this patient
      – true abstinence ***When this is in line with the preferred and usual lifestyle of the subject.*** (~~not including p~~***P***eriodic abstinence ***[eg,*** ~~such as~~ calendar, ovulation, symptothermal, postovulation methods***]***, ***declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception*** ~~or withdrawal~~).

   There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
3. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -5 (Visit S1)
4. Fasting (minimum of 10 hours) calculated LDL-C at Week -5 (Visit S1)
   - Primary prevention ≥130 mg/dL (3.4 mmol/L)
   - Secondary prevention and/or heterozygous familial hypercholesterolemia (HeFH) ≥100 mg/dL (2.6 mmol/L)
   - ***All patients must have fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3)***

   ~~Note: A single repeat of LDL-C may be completed prior to initiation of the single-blind Run-in period. For those patients who have a repeat LDL-C, the mean of the first value and the repeat value will be used to determine eligibility.~~

   ~~For patients taking proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (eg, alirocumab and evolocumab), doses must be administered on a consistent schedule and~~

~~the study lipid values must be obtained within 24-48 hours prior to the next planned dose of the PCSK9 inhibitor.~~

In the case of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor use, the patient must have received 3 stable doses. It is important that lipid values are measured at PCSK9i trough levels. Therefore, study visits should be scheduled in accordance with the patient's PCSK9i injection regimen so that measurement of lipid values for all visits occurs before the PCSK9i injection but not greater than 48 hours before the next scheduled PCSK9i injection. Patients who have discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least 4 months prior to Screening Visit S1.

CHANGE 6 SUBJECT EXCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis; Section 6.2.2, Subject Exclusion Criteria

Original Text:

2. Renal dysfunction or a glomerulonephropathy, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m2 at Week -5 (Visit S1).

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

New Text:

2. Renal dysfunction or a glomerulonephropathy, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m2 at Week -5 (Visit S1).

   Note: A single repeat of eGFR may be completed ~~prior to randomization~~ ***between Visits S1 and S2.*** For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

Original Text:

5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg measured according to local standards.

   Note: At the discretion of the investigator, blood pressure (BP) medications can be adjusted and/or additional assessment of BP may be completed prior to randomization, with the repeat assessment value used to determine eligibility. Alternatively, patients can be rescreened if BP status has changed.

New Text

5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥~~180~~ ***160*** mmHg and/or diastolic blood pressure (DBP) ≥~~110~~ ***100*** mmHg measured according to local standards.

   Note: At the discretion of the investigator, ***the time between Visits S1 and S2 can be extended by 4 weeks for adjustments in*** blood pressure (BP) medications can be adjusted and/or additional assessment of BP ~~may be completed prior to randomization~~, with the repeat assessment value used to determine eligibility. Alternatively, patients can be rescreened if BP status has changed.

Original Text:

19. Planned initiation or changes to the following drugs:
    - Hormone replacement (6 weeks prior to randomization)
    - Thyroid replacement (6 weeks prior to randomization)
    - Diabetes medications (4 weeks prior to randomization)
    - Obesity medication (3 months prior to randomization)
    - PCSK9: Patients who are currently on a stable inhibitor (alirocumab or evolocumab) for at least 3 doses will be included in this study (all lipid values must be obtained 1-2 days prior to the next PCSK9 inhibitor dose to evaluate eligibility and on treatment lipid values). Patients who were previously (either investigational or commercial) on a PCSK9 inhibitor, must have discontinued 4 months prior to screening (Week -5, Visit S1).
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

New Text:

19. Planned initiation or changes to the following drugs:
    - Hormone replacement (6 weeks prior to randomization)
    - Thyroid replacement (6 weeks prior to randomization)
    - Diabetes medications (4 weeks prior to randomization)
    - Obesity medication (~~3 months~~***4 weeks*** prior to randomization)
    - PCSK9 ***inhibitors***: Patients who are currently on a stable ***commercially available PCSK9*** inhibitor (alirocumab or evolocumab) ~~for~~ ***must have had*** at least 3 doses ***prior to Visit S1.***~~will be included in this study (all lipid values must be obtained 1-2 days prior to the next PCSK9 inhibitor dose to evaluate eligibility and on treatment lipid values)~~. Patients who were previously (either investigational or

commercial) on a PCSK9 inhibitor, must ~~have discontinued~~ ***wait at least*** 4 months ***after last dose*** prior to screening (Week -5, Visit S1).

20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
22. ***Pregnant, breastfeeding, or intending to become pregnant within 30 days after last dose of study drug.***
23. ***Patients who have enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9 are excluded.***
24. ***In patients taking very low dose statins, gemfibrozil is excluded per the co-administration prescribing instructions***

CHANGE 7 PATIENT IDENTIFICATION, RANDOMIZATION, AND BLINDING REVISION

Location:

Section 6.3, Patient Identification, Randomization, and Blinding

Original Text:

Patient identification numbers will be assigned sequentially by interactive web response system (IWRS) at the time of informed consent during the screening module transaction. The patient numbers will be an [redacted]

For patients who satisfy all entry criteria and complete the 5-week screening period, randomization will occur at Week 0 (Visit T1), and their randomization number will be assigned via IWRS. Patients will be stratified on primary prevention or secondary prevention and randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- bempedoic acid 180 mg or
- matching placebo

New Text:

Patient identification numbers will be assigned sequentially by interactive web response system (IWRS) at the time of informed consent during the screening module transaction. ~~The patient numbers will be an~~ [redacted]

For patients who satisfy all entry criteria and complete the 5-week screening period, randomization will occur at Week 0 (Visit T1) ~~and their randomization number will be assigned via IWRS~~. Patients will be stratified on primary prevention or secondary prevention and randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- bempedoic acid 180 mg or
- matching placebo

CHANGE 8 ADMINISTRATION OF INVESTIGATIONAL MEDICINAL PRODUCT

Location:

Section 7.2, Administration of Investigational Medicinal Product

Original Text:

Table 1: Investigational Product

	Investigational Medicinal Product	
Product Name:	Bempedoic acid	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure[a]:	100-count bottle with screw on, child proof cap	35- or 100-count bottle (depending upon visit) with screw on, child proof cap
Route of Administration:	Oral, once per day, with or without food	Oral, once per day, with or without food
Physical Description:	[redacted]	
Manufacturer (Fill/Finish):		

[a] A 100-day supply of study drug will be included in the 100-count bottle and a 35-day supply of single blind placebo will be included in the 35-count bottle.

New Text:

Table 1: Investigational Product

	Investigational Medicinal Product	
Product Name:	Bempedoic acid	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure[a]:	100-count bottle with screw on, child-proof cap	35- or 100-count bottle (depending upon visit) with screw on, child-proof cap
Route of Administration:	Oral, once per day, with or without food	Oral, once per day, with or without food
Physical Description:	[redacted]	
~~**Manufacturer (Fill/Finish):**~~		

[a] A 100-day supply of study drug will be included in the 100-count bottle and a 35-day supply of single blind placebo will be included in the 35-count bottle.

CHANGE 9 LIPID-REGULATING MEDICATIONS AND SUPPLEMENTS REVISIONS

Location:

Section 7.3.1, Lipid-Regulating Medications and Supplements

Original Text:

Patients are allowed to continue their background lipid-lowering therapy during this study as long as the drugs and doses are stable for 4 weeks prior to screening. Use of fibrates must be stable at least 6 weeks prior to screening (Week -5 Visit S1). Screening lipid values and other assessments of lipids must be within 24-48 hours of the next dose if a patient is taking a PCSK9 inhibitor. Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies and include:

New Text:

Patients are allowed to continue their background lipid-lowering therapy during this study as long as the drugs and doses are stable for 4 weeks prior to screening ***(at least 3 doses are required for PCSK9 inhibitors)***. Use of fibrates must be stable at least 6 weeks prior to screening (Week -5 Visit S1). ~~Screening lipid values and other assessments of lipids must be within 24-48 hours of the next dose if a patient is taking a PCSK9 inhibitor.~~ Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies and include:

Original Text:

Fibrates

- Fenofibrate (Antara®, Lofibra®, Tricor®, Triglide™, Lipantil®, Supralip®)
- Bezafibrate (Bezalip®)
- Ciprofibrate (Modalim®)
- Gemfibrozil (Lopid®)

New Text:

Fibrates

- Fenofibrate (Antara®, Lofibra®, Tricor®, Triglide™, Lipantil®, Supralip®)*****
- Bezafibrate (Bezalip®)
- Ciprofibrate (Modalim®)
- ~~Gemfibrozil (Lopid®)~~

**** Note that gemfibrozil (lopid®) is exclusionary in patients taking a very low dose statin as per co-administration prescribing instructions.***

CHANGE 10 PROHIBITED MEDICATIONS REVISIONS

Location:

Section 7.3.2, Prohibited Medications

Original Text:

The use of the following medications and/or supplements are prohibited during the study.

- Statins at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg
- New or planned dose changes of systemic corticosteroids.

  Note: Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks from Visit S1). Topical steroids are allowed.

- Red yeast rice (monacolin K) extract and Berberine-containing products must be discontinued 2 weeks prior to screening (Week -5, Visit S1).
- Lomitapide or apheresis therapy within 3 months to screening (Week -5, Visit S1).
- Mipomersen within 6 months to screening (Week -5, Visit S1).
- CETP-I within the last 2 years to screening (Week -5, Visit S1) except for Evaceptrapib within the last 3 months to screening (Week -5, Visit S1).
- New or planned anti-arrhythmia medication(s) within 3 months to screening (Week -5, Visit S1).
- Any experimental or investigational drugs within 30 days to screening (Week -5, Visit S1).

New Text:

The use of the following medications and/or supplements are prohibited during the study.

- Statins at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg
- New or planned dose changes of systemic corticosteroids.

  Note: Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks from Visit S1). Topical ***and inhaled*** steroids are allowed.
- Red yeast rice (monacolin K) extract and Berberine-containing products must be discontinued 2 weeks prior to screening (Week -5, Visit S1).
- Lomitapide or apheresis therapy within 3 months to screening (Week -5, Visit S1).
- Mipomersen within 6 months to screening (Week -5, Visit S1).
- CETP-I within the last 2 years to screening (Week -5, Visit S1) except for Evaceptrapib within the last 3 months to screening (Week -5, Visit S1).
- New or planned anti-arrhythmia medication(s) within 3 months to screening (Week -5, Visit S1).
- ***Previous enrollment into a study of an experimental siRNA of PCSK9 or use of a***~~A~~Any experimental or investigational drugs within 30 days to screening (Week -5, Visit S1).
- ***Gemfibrozil in patients taking a very low dose statin as per co-administration prescribing instructions.***

CHANGE 11 ALLOWABLE MEDICATIONS REVISIONS

Location:

Section 7.3.3, Allowable Medications

Original Text:

Patients must be on stable concomitant medication regimen(s) for the following medications and/or supplements:

- Hormone replacement therapy within 6 weeks of randomization
- Thyroid replacement therapy within 6 weeks of randomization. Diabetic medication(s) within 4 weeks of randomization.
- Obesity medication(s) within 3 months of randomization.
- Oral lipid-modifying therapy within 4 weeks to screening (Week -5, Visit S1).
- PCSK9 inhibitors (alirocumab or evolocumab) for at least 3 doses will be included in this study (all lipid values must be obtained 1-2 days prior to the next PCSK9 inhibitor dose to evaluate eligibility and on treatment lipid values). Patients who were previously (either investigational or commercial) on a PCSK9 inhibitor, must have discontinued 4 months prior to screening (Week -5, Visit S1)
- Hypertensive medication(s) within 2 weeks prior to randomization.
- Hypertriglyceridemia medication(s) within 4 weeks prior to screening (Week -5, Visit S1)

New Text:

Patients must be on stable concomitant medication regimen(s) for the following medications and/or supplements:

- Hormone replacement therapy within 6 weeks of randomization
- Thyroid replacement therapy within 6 weeks of randomization. Diabetic medication(s) within 4 weeks of randomization.
- Obesity medication(s) within ~~3 months~~***4 weeks*** of randomization.
- Oral lipid-modifying therapy within 4 weeks to screening (Week -5, Visit S1).
- PCSK9 inhibitors (alirocumab or evolocumab) ~~for~~ ***if*** at least 3 doses ~~will be included in this study (all lipid values must be obtained 1-2 days~~ prior to ***Visit S1***~~the next PCSK9 inhibitor dose to evaluate eligibility and on treatment lipid values)~~. Patients who were previously (either investigational or commercial) on a PCSK9 inhibitor, must have discontinued 4 months prior to screening (Week -5, Visit S1)
- Hypertensive medication(s) within 2 weeks prior to randomization.
- Hypertriglyceridemia medication(s) within 4 weeks prior to screening (Week -5, Visit S1) ***with the exception of fibrates that are within 6 weeks prior to screening (Week -5, Visit S1)***

CHANGE 12 TREATMENT COMPLIANCE REVISION

Location:

Section 7.5, Treatment Compliance

Original Text:

Placebo Run-In Adherence to Study Medication

At visits Week -1 (S1) and Week 0 (T1), designated clinical site staff will assess patient study drug compliance by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. If at the Week -1 (S1) visit the patient has not taken all doses of study drug(s) as instructed, the patient will be queried for a reason, findings will be documented, and the patient will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. If at the T1 visit, the average study drug compliance from the placebo run-in period is <80%, or if the patient experiences an adverse event related to the run-in single blind placebo, the patient will not go onto randomization.

New Text:

Placebo Run-In Adherence to Study Medication

At visits Week -1 (~~S1~~***S3***) and Week 0 (T1), designated clinical site staff will assess patient study drug compliance by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. If at the Week -1 (~~S1~~***S3***) visit the patient has not taken all doses of study drug(s) as instructed, the patient will be queried for a reason, findings will be documented, and the patient will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. If at the T1 visit, the average study drug compliance from the placebo run-in period is <80%, or if the patient experiences an adverse event related to the run-in single blind placebo, the patient will not go onto randomization.

CHANGE 13 INFORMED CONSENT

Location:

Section 8.1, Informed Consent

Original Text:

The patient must be adequately informed of the nature and risks of the study and understand the informed consent document (ICD). No study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Participation in banking of samples for genetic analysis is optional for all patients, and consent for this must be documented in the patient's written informed consent.

New Text:

The patient must be adequately informed of the nature and risks of the study and understand the informed consent document (ICD). No study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). ~~Participation in banking of samples for genetic analysis is optional for all patients, and consent for this must be documented in the patient's written informed consent.~~

CHANGE 14 CONFIRMATION OF STATIN INTOLERANCE REVISIONS

Location:

Section 8.2, Confirmation of Statin Intolerance (SI)

Original Text:

Documentation of prior statin use will be based on patient recall and copies of relevant medical records and pharmacy records if readily available. If investigator is unable to assess prior statin use due to poor patient recall and/or lack of relevant medical records, and if appropriate according to local medical practice, documentation of contact with primary care physician regarding prior statin use should be obtained. All available prior statin use history will be recorded in the eCRF. Additionally, the basis for the investigator's confirmation of the patient's SI will be noted in the eCRF.

New Text:

Documentation of prior statin use will be based on patient recall and copies of relevant medical records and pharmacy records if readily available. If investigator is unable to assess prior statin use due to poor patient recall and/or lack of relevant medical records, and if appropriate according to local medical practice, documentation of contact with primary care physician regarding prior statin use should be obtained. ***At minimum, there will need to be documentation for the name of 2 statins and low dose of at least 1 statin to ensure inclusion criteria is met.*** All available prior statin use history will be recorded in the eCRF. Additionally, the basis for the investigator's confirmation of the patient's SI will be noted in the eCRF.

CHANGE 15 PROCEDURE AND SCHEDULE OF ASSESSMENTS REVISIONS

Location:

Section 8.3, Procedure and Schedule of Assessments

Original Text:

Table 2: Schedule of Events (Subject Visit Schedule)

Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28 ±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169 ±7**
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
Statin Intolerance Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight[4]	X			X			X	X
Height/BMI	X							
12-Lead ECG[5]			X					X
Vital Signs[6]	X	X	X	X	X		X	X
Serology[7]	X							
Serum Pregnancy[8]	X							
Urine Pregnancy[9]				X				
TSH	X							
Clinical Safety Labs[10]	X		X	X	X		X	X

Table 2: Schedule of Events (Subject Visit Schedule)

Visit	S1[1,2]	S2	S3	T1	T2	T3/phone	T4	T5/EOS[3]
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28 ±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169 ±7**
Basic Fasting Lipids[11]	X		X	X	X		X	X
HbA_{1C}	X			X			X	X
10 mL reserve sample				X				X
PK sample				X	X		X	X
Pharmacogenomic sample (optional)				X				
apoB				X			X	X
hs-CRP				X			X	X
Diet and exercise counseling[12]	X	X	X	X	X	X	X	
Establish Patient Eligibility		X		X				
Randomization				X				
IWRS Contact[13]	X	X		X			X	X
Single-blind Drug Dispensing		X						
Double-blind Drug Dispensing				X			X	
Drug Return/Compliance			X	X	X		X	X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visits, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T5 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

[1] An optional basic fasting (minimum of 10 hours) lipid MAY be completed at Visit S2 (prior to starting single-blind medication) if patient fails to meet lipid entry criterion at Visit S1,The mean of the first value and the repeat value will be used to determine eligibility.

[2] A recheck of blood pressure may be completed at Visit S2 if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (diastolic blood pressure [DBP] and/or systolic blood pressure [SBP]) do not meet exclusionary values. Repeat labs may be completed at Visit S2 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

[4] Body weight will be measured while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[5] Single 12-lead ECG will be performed prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

[7] Serology for HbsAg, HCV-ABVivi.

[8] Pregnancy test completed in women of child-bearing potential only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. A coagulation panel will be completed for all patients at Week -5 (Visit S1). A coagulation panel will be completed only for patients on vitamin K antagonists at Day 1 (Visit T1) and 3 to 5 days later. Please refer to laboratory manual for detailed schedule of tests.

[10] Basic fasting (minimum of 10 hours) lipids include total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

[11] Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

[12] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

New Text:

Table 2: Schedule of Events (Subject Visit Schedule)

Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28 ±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169 ±7**
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
Statin Intolerance Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight[4]	X			X			X	X
Height/BMI	X							
12-Lead ECG[5]			X					X
Vital Signs[6]	X	X	X	X	X		X	X
Serology[7]	X							
Serum Pregnancy[8]	X							
Urine Pregnancy[9]				X				
TSH	X							
Clinical Safety Labs[10]	X		X	X	X		X	X

Table 2: Schedule of Events (Subject Visit Schedule)

Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28 ±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169 ±7**
Basic Fasting Lipids[11]	X		X	X	X		X	X
HbA_{1C}	X			X			X	X
~~10 ml reserve sample~~				~~X~~				~~X~~
PK sample				~~X~~	X		X	X
~~Pharmacogenomic sample (optional)~~				~~X~~				
apoB				X			X	X
hs-CRP				X			X	X
Diet and exercise counseling[12]	X	X	X	X	X	X	X	
Establish Patient Eligibility		X		X				
Randomization				X				
IWRS Contact[13]	X	X		X			X	X
Single-blind Drug Dispensing		X						
Double-blind Drug Dispensing				X			X	
Drug Return/Compliance			X	X	X		X	X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visits, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). ~~For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AE (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to the clinic or by phone), Visit T5 will be considered the End of Study (EOS)/Earthly Withdrawal from study and no further visits will be scheduled.~~

[1] An optional ~~basic~~ fasting (minimum of 10 hours) ~~lipid~~ ***TG assessment*** MAY be completed ***between Visits S1and*** ~~at visit~~ S2 (prior to starting single-blind medication) if patient fails to meet ~~lipid only~~ TG criterion at Visit S1. The ~~mean of the first~~ ***repeat*** value ~~and the repeat value~~ will be used to determine eligibility.

[2] A recheck of blood pressure may be completed ~~at~~ ***between Visits S1 and*** ~~Visit~~ S2 if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (diastolic blood pressure [DBP] and/or systolic blood pressure [SBP]) do not meet exclusionary values. Repeat labs may be completed between Visit S1 and Visit S2 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

[4] Body weight will be measured while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[5] Single 12-lead ECG will be performed prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

[7] Serology for HbsAg, HCV-ABVivi.

[8] Pregnancy test completed in women of child-bearing potential only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

[***9***] ***Urine pregnancy test completed in women of child-bearing potential only just prior to randomization.***

[~~10~~***9***] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. A coagulation panel will be completed for all patients at Week -5 (Visit S1). A coagulation panel will be completed only for patients on vitamin K antagonists at Day 1 (Visit T1) and 3 to 5 days later. ***For these visits, the sample may be analyzed at either the central or a local lab.*** Please refer to laboratory manual for detailed schedule of tests.

[11] Basic fasting (minimum of 10 hours) lipids include total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides. ~~Repeat within 1 week if exceed protocol specified criteria.~~

[12] Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

[13] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

CHANGE 16 SCREENING WEEK -5 REVISIONS

Location:

Section 8.3.1, Screening Week -5

Original Text:

8.3.1. Screening Week -5 (Visit S1; Day -63 to -29)

New Text:

8.3.1. Screening Week -5 (Visit S1; Day ~~-63 to -29~~ *-35* ±*7* days)

Original Text:

The screening period can be extended an additional 4 weeks if needed to adjust background therapy or other reasons.

New Text:

The screening period ***(between Visits S1 and S2)*** can be extended an additional 4 weeks if needed to adjust background therapy or other reasons.

Patients who are considered to be screen failures due to not meeting stability requirements for a condition or concurrent medication may be considered for rescreening after consultation with the Sponsor (or designee). These patients must be re-consented, re-registered in the IWRS, and will have a new patient ID number assigned.

CHANGE 17 SCREENING VISITS REVISIONS

Location:

Section 8.3.3, Screening Week -1 (Visit S3; Day -7 ±3)

Original Text:

The patient will undergo the following assessments and procedures at Visit S3:

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints (starting from signing the informed consent document)
3. 12-lead electrocardiogram (ECG)
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
6. Diet and exercise counseling
7. Study drug compliance assessment

New Text:

The patient will undergo the following assessments and procedures at Visit S3:

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints (starting from signing the informed consent document)
3. 12-lead electrocardiogram (ECG)
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG). ***LDL-C value must be ≥70 mg/dL.***
6. Diet and exercise counseling
7. Study drug compliance assessment

CHANGE 18 WEEK 0 VISIT REVISION

Location:

Section 8.3.4, Week 0 (Visit T1; Day 1)

Original Text:

Prior to scheduling Visit T1, review the screening clinical results to determine whether the patient continues to meet lab eligibility criteria. At Visit T1, determine whether the patient was adherent with placebo treatment during the run-in period (average of ≥80% adherence required) and had no issues with tolerability of run-in period study medication. Patients with intolerable side effects, including but not limited to muscular skeletal pain, will be run-in failures.

If the patient has met all inclusion criteria and none of the exclusion criteria, the patient may be randomized into the double-blind treatment period. Patients who fail to meet all entry criteria after initiation of single-blind placebo run-in are considered to be run-in failures and will not be randomized.

Patients are considered randomized once all eligibility criteria are confirmed and a randomization number is obtained by the IWRS on the day of first dose.

7. Central clinical laboratory evaluations:
   - Coagulation in patients on vitamin K antagonists
   - Hematology, blood chemistry, and urinalysis
   - 10-mL reserve sample
   - apoB

- hs-CRP
- HbA_{1C}
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Predose PK sample

8. Urine pregnancy in women of childbearing potential only prior to randomization.
9. Diet and exercise counseling
10. IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
11. Dispense double-blind study drug and ingestion of first dose and provide dosing and storage instructions

New Text:

Prior to scheduling Visit T1, review the screening clinical results to determine whether the patient continues to meet lab eligibility criteria. At Visit T1, determine whether the patient was adherent with placebo treatment during the run-in period (average of ≥80% adherence required) and had no issues with tolerability of run-in period study medication. Patients with intolerable side effects, including but not limited to muscular skeletal pain, will be run-in failures.

If the patient has met all inclusion criteria and none of the exclusion criteria, the patient may be randomized into the double-blind treatment period. Patients who fail to meet all entry criteria after initiation of single-blind placebo run-in are considered to be run-in failures and will not be randomized.

Patients are considered randomized once all eligibility criteria are confirmed and ~~a randomization number is obtained by the IWRS~~ ***IWRS is contacted with confirmation of patient randomization*** on the day of first dose.

7. Central clinical laboratory evaluations:
    - Coagulation in patients on vitamin K antagonists ***(return 3-5 days after Visit T1 for repeat coagulation). Coagulation samples for this visit may be analyzed at the central or local lab.***
    - Hematology, blood chemistry, and urinalysis
    - ~~10-mL reserve sample~~
    - apoB
    - hs-CRP
    - HbA_{1C}
    - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
    - ~~Predose PK sample~~
8. Urine pregnancy in women of childbearing potential only prior to randomization.

9. Diet and exercise counseling
10. IWRS ~~contact to obtain the patient randomization number and MED ID number~~ ***contact to randomize patient and assign bottle number(s)*** for double-blind study drug
11. Dispense double-blind study drug and ingestion of first dose and provide dosing and storage instructions

CHANGE 19 TREATMENT WEEK 4 AND 12 REVISIONS

Location:

Section 8.3.5, Treatment Week 4 (Visit T2; Day 29 ±3 days);
Section 8.3.7 Treatment Week 12 (Visit T4; Day 85 ±3 days)

Original Text:

Patients will undergo the following assessments and procedures at Week 4 (Visit T2):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints
3. Weight
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
   - PK Sample

New Text:

Patients will undergo the following assessments and procedures at Week 4 (Visit T2):

1. Concomitant medication review (ongoing)
2. Assess AEs, SAEs, and potential clinical endpoints
3. Weight
4. Vital signs
5. Central clinical laboratory evaluations:
   - Hematology, blood chemistry, and urinalysis
   - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
   - PK Sample ***prior to dose***

CHANGE 20 WEEK 24/EOS REVISION

Location:

Section 8.3.8, Treatment Week 24/EOS (Visit T5; Day 169 ±7 days)

Original Text:

- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- PK Sample
- Reserve Sample

New Text:

- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- PK Sample ***before dose***
- ~~Reserve Sample~~

CHANGE 21 EARLY WITHDRAWAL REVISION

Location:

Section 8.4, Early Withdrawal from Study or Treatment

Original Text:

Patients who withdraw from study drug prior to Week 24 (Visit T5) for any reason will be asked to continue to be followed for safety assessments, including basic fasting lipids, at clinic visit following the protocol-specified visit schedule (see Section 8.3). Protocol procedures to be completed for patients who consent will include those specified at each visit as noted in Schedule of Events (see Section 8.3).

New Text:

Patients who withdraw from study drug prior to Week 24 (Visit T5) for any reason will be asked to continue to be followed for safety assessments, including basic fasting lipids, at clinic visit following the protocol-specified visit schedule (see Section 8.3). ~~Protocol procedures to be completed for patients who consent will include those specified at each visit as noted in Schedule of Events (see Section 8.3)~~

CHANGE 22 OVERDOSE INFORMATION ADDED

Location:

New section

Original Text:

Not applicable.

New Text:

8.5. Overdose

There is no specific antidote for an overdose of bempedoic acid. Management of an overdose should be focused on the treatment of symptoms. These symptoms should be managed according to current standards of care with appropriate supportive measures. Also discontinuation of study drug should be considered, based on medical judgement.

CHANGE 23 PHYSICAL EXAMINATION REVISIONS

Location:

Section 10.1.4, Physical Examination

Original Text:

Documentation of the PE findings will be included in the source documentation at the clinical site. Significant findings prior to the start of study drug will be recorded on the Medical History/Current Medical Conditions page of the eCRF. Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

New Text:

Documentation of the PE findings will be included in the source documentation at the clinical site. Significant findings ~~prior to the start of study drug~~ ***noted at Visit S2*** will be recorded on the Medical History/Current Medical Conditions page of the eCRF. Only changes from ***Visit S2*** ~~baseline~~ physical examination findings ***(or other unscheduled physical exams performed after informed consent but prior to randomization)*** that meet the definition of an AE will be recorded on the AE page of the eCRF.

CHANGE 24 CLINICAL LABORATORY TESTS REVISIONS

Location:

Section 10.1.6.1, Laboratory Parameters (Safety)

Original Text:

Table 4: Clinical Laboratory Parameters (Safety)

<table>
<tr><th>Clinical Laboratory Test</th><th>Clinical Laboratory Test</th></tr>
<tr><td><u>Hematology</u>
Hematocrit (Hct)
Hemoglobin (Hgb)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelet count
Red blood (RBC) cell count
White blood (WBC) cell count with differential (absolute and %)</td><td rowspan="2"><u>Blood Chemistry (serum, fasting)</u>
Albumin (Alb)
Alkaline phosphatase (Alk-P)
Alanine aminotransferase (ALT; SGPT)
Aspartate aminotransferase (AST; SGOT)
Blood urea nitrogen (BUN)
Calcium (Ca)
Carbon dioxide (CO_2)
Chloride (Cl)
Creatinine
Creatine kinase (CK)
Glucose
Lactate dehydrogenase (LDH)
Phosphorus
Potassium (K)
Sodium (Na)
Total and direct bilirubin (TB)
Total protein
Uric acid</td></tr>
<tr><td><u>Urinalysis (Dipstick)</u>
Clarity
Bilirubin
Color
Glucose
Ketones
Leukocyte esterase
Nitrate
Occult blood
pH
Protein
Specific gravity
Urobilinogen
Urine Pregnancy in females of child bearing potential</td></tr>
<tr><td><u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u>
Bacteria
Casts
Crystals
Epithelial cells
Red blood cell (RBC)
WBC</td><td><u>Coagulation – all patients at Visit S1; only in patients receiving vitamin K antagonists at Visit T1 and 3 to 5 days post Visit T1 using local or central lab</u>
Prothrombin time (PT)
International normalized ratio (INR)</td></tr>
</table>

Table 4: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) • Serum pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) • Thyroid-stimulating hormone (TSH)	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • Reserve blood samples for potential future measurement of bempedoic acid safety or pharmacodynamic biomarkers • Reserve genetic blood sample (optional)

New text

Table 4: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	**Clinical Laboratory Test**
Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %)	Blood Chemistry (serum, fasting) • Albumin (Alb) • Alkaline phosphatase (Alk-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitr*i*te • Occult blood • pH • Protein • Specific gravity • Urobilinogen • Urine Pregnancy in females of child bearing potential	

Table 4: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Coagulation – all patients at Visit S1; only in patients receiving vitamin K antagonists at Visit T1 and 3 to 5 days post Visit T1 using local or central lab • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) • Serum pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) • Thyroid-stimulating hormone (TSH)	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • ~~Reserve blood samples for potential future measurement of bempedoic acid safety or pharmacodynamic biomarkers~~ • ~~Reserve genetic blood sample (optional)~~

Location:

Section 10.1.6.2, Clinical Laboratory Tests (PK)

Original Text:

A PK blood sample will be collected prior to dosing at Visits T1, T2, T4, and T5.

Patients will be in a seated position during the blood collection. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping are described in Section 10.1.6.3.

New Text:

A PK blood sample will be collected prior to dosing at Visits ~~T1~~, T2, T4, and T5.

Patients will be in a seated position during the blood collection. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping are described in Section 10.1.6.3.

Location:

Section 10.1.6.3, Sample Collection, Storage, and Shipping

Original Text:

Clinical laboratory and PK samples will be collected by appropriate clinical site personnel and then shipped according to a separate laboratory manual provided by the Central Laboratory.

Samples will be processed by the Central Laboratory, and PK samples will be forwarded to the Bioanalytical Laboratory for analysis. Reserve samples will be stored frozen for potential future measurement of additional bempedoic acid safety and efficacy biomarkers. A reserve genetic blood sample (optional) will also be stored frozen for potential future bempedoic acid genetic analyses.

New Text:

Clinical laboratory and PK samples will be collected by appropriate clinical site personnel and then shipped according to a separate laboratory manual provided by the Central Laboratory. Samples will be processed by the Central Laboratory, and PK samples will be forwarded to the Bioanalytical Laboratory for analysis. ~~Reserve samples will be stored frozen for potential future measurement of additional bempedoic acid safety and efficacy biomarkers. A reserve genetic blood sample (optional) will also be stored frozen for potential future bempedoic acid genetic analyses.~~

Location:

Section 10.1.6.5, Exploratory Biomarker Measurement; Section 10.1.6.6, Genetic Testing

Original Text:

10.1.6.5 Exploratory Biomarker Measurement

Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from reserve samples.

10.1.6.6 Genetic Testing

As part of this study, all patients will be invited to provide a blood sample to be banked for potential future genetic analyses. Participation in this portion of the study is optional and a sample will only be obtained if consent is provided. Those who choose not to provide a sample for genetic analysis may still participate in the main portion of the study. Samples will be anonymized before testing to assure that the results cannot be traced back to an individual patient.

New Text:

~~**10.1.6.5 Exploratory Biomarker Measurement**~~

~~Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from reserve samples.~~

~~**10.1.6.6 Genetic Testing**~~

~~As part of this study, all patients will be invited to provide a blood sample to be banked for potential future genetic analyses. Participation in this portion of the study is optional and a sample will only be obtained if consent is provided. Those who choose not to provide a sample for genetic analysis may still participate in the main portion of the study. Samples will be anonymized before testing to assure that the results cannot be traced back to an individual patient.~~

CHANGE 25 ADVERSE EVENT REPORTING REVISIONS

Location:

Section 10.2.3, Reporting

Original Text:

All AEs occurring during the course of the study (starting from signing informed consent to study completion) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the Investigator. Beginning with Visit S2 (Week -4), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

New Text:

All AEs occurring during the course of the study (starting from signing informed consent to study completion ***or discontinuation***) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the Investigator ***through 30 days following the last dose of study drug.*** Beginning with Visit S2 (Week -4), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. ***Any SAE that occurs from the time of ICF through 30 days following the last dose of study drug should be reported to the Sponsor per Section 10.2.7.4.***

CHANGE 26 DEFINITION OF SAE REVISIONS

Location:

New sections

Original Text:

Not applicable.

New Text:

10.2.7.2 Definition of Serious Adverse Events or Outcomes not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- ***Preplanned or elective hospitalization including social and/or convenience situations (eg, due to inclement weather)***
- ***Overdose of either Esperion study drug or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page***

10.2.7.3 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the central (or local where appropriate) laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. For criteria of reporting abnormal lab values as AE, see Section 10.1.6.4.

Location:

10.2.7.2, Reporting of Serious Adverse Events

Original Text:

10.2.7.2 Reporting of Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following study completion or study discontinuation, must be reported by the Principal Investigator or designee to the Safety designee within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. All SAEs that the Investigator considers related to study drug that occur after the 30-day follow-up of the study period must be reported to the Sponsor.

The Investigator is required to submit SAE reports to the IRB/IEC in accordance with local requirements. All Investigators involved in studies using the same investigational product will receive any safety alert notifications for onward submission to their local IRB as required. All reports sent to Investigators will be blinded.

***~~10.2.7.2~~10.2.7.4* Reporting of Serious Adverse Events**

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following ~~study completion or study discontinuation~~ ***last dose of study drug,*** must be reported by the Principal Investigator or designee to the Safety designee within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. All SAEs that the Investigator considers related to study drug that occur after the 30-day follow-up of the study period must be reported to the Sponsor.

To report the SAE, complete the SAE information in the clinical EDC database within 24 hours of becoming aware of the occurrence. Additional information, such as diagnostic test results or hospital discharge summary can be sent via email (drugsafety@esperion.com) or via fax (+1-734-887-3988).

The Investigator is required to submit SAE reports to the IRB/IEC in accordance with local requirements. All Investigators involved in studies using the same investigational product will receive any safety alert notifications for onward submission to their local IRB as required. All reports sent to Investigators will be blinded.

CHANGE 27 REPORTS OF PREGNANCY REVISIONS

Location:

Section 10.2.7.4, Reports of Pregnancy

Original Text:

10.2.7.4. Reports of Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor/SAE designee using the Pregnancy Report Form within the same timelines as an SAE.

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to the Sponsor.

Adverse events or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms.

Patients who become pregnant will discontinue Investigational Medicinal Product (IMP) immediately and complete the end of study evaluations.

New Text:

~~10.2.7.4~~*10.2.7.6*. Reports of Pregnancy

If a patient becomes pregnant during the study ***or within 30 days of the last dose of study drug***, the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the Sponsor/SAE designee using the ***paper*** Pregnancy Report Form within the same timelines as an SAE.

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the ***paper*** Pregnancy Outcome Report Form should be completed and reported to the Sponsor.

Adverse events or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE~~or SAE forms~~ ***CRF***.

Patients who become pregnant will discontinue Investigational Medicinal Product (IMP) immediately and complete the end of study evaluations.

CHANGE 28 HEPATIC FUNCTION REVISIONS

Location:

Section 10.2.11.3.2, Hepatic Function

Original Text:

- If repeat LFT assessment confirms ALT and/or AST >5 × ULN, patient should be withdrawn from study drug treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3)
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further treatment with study drug, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3):

New Text:

- If repeat LFT assessment confirms ALT and/or AST >5 × ULN, patient should be withdrawn from study drug treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3) ***or more frequently if deemed appropriate by the Investigator.***

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further treatment with study drug, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Section 8.3) ***or more frequently if deemed appropriate by the Investigator.***

CHANGE 29 MUSCLE-RELATED EVENTS REVISIONS

Location:

Section 10.2.11.3.3, Muscle-Related Events

Original Text:

Repeat CK assessment will include query for related symptoms.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic the investigator with input from the Sponsor may consider continuing study medication with continued CK assessments every 1-2 weeks.

New Text:

Repeat CK assessment will include query for related symptoms.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic the ***patient should receive further assessment and investigation into the cause, assess whether there is renal injury and measure CK approximately weekly or more frequently if clinically indicated until resolution. If CK levels continue to rise; IMP should be discontinued***. ~~investigator with input from the Sponsor may consider continuing study medication with continued CK assessments every 1-2 weeks.~~

CHANGE 30 STATISTICAL METHODS REVISIONS

Location:

Section 2, Synopsis; Section 11.1, General Considerations

Original Text:

The statistical analyses described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the first time that the DMC reviews data for this study. The SAP will supersede the protocol in the event of any differences between the 2 documents in relation to data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

New Text:

The statistical analyses described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP~~), which will be finalized prior to the first time that the~~

~~DMC reviews data for this study~~. The SAP will supersede the protocol in the event of any differences between the 2 documents in relation to data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

CHANGE 31 PRIMARY AND SECONDARY ENDPOINT AND SAFETY ANALYSES

Location:

Section 2, Synopsis; Section 11.5, Primary Endpoint Analysis; Section 11.6, Secondary and Tertiary Endpoint Analysis; Section 11.7, Safety Analysis

Original Text:

11.5 Primary Endpoint Analysis

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. Baseline is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1).

The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received.

Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). The primary analysis will be that from the PMM, while the observed case analysis will be confirmatory. The PMM will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Patients with missing LDL-C data at Week 12 who are no longer taking study treatment can be assumed to no longer be benefitting from study medication, and their missing value(s) can be assumed to be returning toward their baseline value. In this instance, it is reasonable to impute LDL-C values based on the patients' baseline value. Patients with missing LDL-C data at Week 12 who are still taking study treatment can be assumed to continue to benefit from study medication, and their missing value(s) can be assumed to be similar to those who remain on study treatment and have data. In this instance, it is reasonable to impute LDL-C values based on the observed values in their randomized treatment group at Week 12. To account for uncertainty, missing values will be imputed using multiple imputation. Imputed datasets will be analyzed using an ANCOVA model with the treatment and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. Approximately 100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

11.6 Secondary and Tertiary Endpoint Analysis

Secondary efficacy endpoints are also of interest for this study, in terms of controlling the overall Type I error rate, a gatekeeping or stepdown approach will be used to test the primary efficacy endpoint and then specific secondary efficacy endpoints sequentially in order to preserve the study-wise Type I error rate. The sequence for the stepdown procedure in this study is as follows:

6. Test the primary efficacy endpoint: percent change from baseline to Week 12 in LDL-C
7. Test the percent change from baseline to Week 24 in LDL-C
8. Test the percent change from baseline to Week 12 in non-HDL-C
9. Test the percent change from baseline to Week 12 in TC
10. Test the percent change from baseline to Week 12 in apoB
11. Test the percent change from baseline to Week 12 in hs-CRP

In this hierarchical testing structure, each hypothesis is tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. If the primary endpoint meets the criteria for statistical significance, then the percent change from baseline to Week 24 in LDL-C will be tested; and so forth.

For the remaining secondary efficacy endpoints and the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints, the p-values for those endpoints will be considered descriptive.

Percent change from baseline to Week 24 in LDL-C; change from baseline to Weeks 12 and 24 in LDL-C; percent change from baseline to Weeks 12 [redacted] in [redacted] non-HDL-C, [redacted] and TC; and percent change from baseline to Weeks 12 [redacted] in apoB and hs-CRP will each be analyzed using ANCOVA with treatment group and patient type (primary prevention; secondary prevention) as factors and the relevant baseline as a covariate. Baseline for [redacted] non-HDL-C, [redacted] and TC is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value. Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Only observed case data will be included in each analysis (no imputation will be performed for missing data). For each lipid parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For all continuous efficacy endpoints (percent change from baseline in LDL-C, [redacted] non-HDL-C, TC, [redacted] apoB, and hs-CRP; change from baseline in LDL-C; to Week 12 and 24, as appropriate), the ANCOVA assumption of normality will be assessed. If non-normality of the data is found at any time point for any parameter, either the data will be transformed so that it is normally distributed or a nonparametric test will be used instead of the planned ANCOVA.

Finally, the number and percent of patients in each treatment group requiring additional (post-randomization) TG-lowering therapy will be summarized. The medications will be summarized by treatment group.

11.7 Safety Analysis

No statistical analyses will be performed on any of the safety data in this study.

The summarization of AEs will include TEAEs, defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not related to the product. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. These AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

New Text:

11.5 Primary Endpoint Analysis

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. Baseline is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1).

The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. ***The details of the ANCOVA model and options to account for unequal variances and group size will be described in the SAP.***

Missing data for the primary endpoint will be imputed using a multiple imputation method that accounts for treatment adherence. ~~Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). The primary analysis will be that from the PMM, while the observed case analysis will be confirmatory. The~~ ***A pattern mixture model (***PMM***)*** will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Patients with missing LDL-C data at Week 12 who are no longer taking study treatment can be assumed ~~to~~ no longer ***to*** be benefitting from study medication, and their missing value(s) can be assumed to be ~~returning toward their baseline value~~ ***similar to those from placebo patients***. In this instance, it is reasonable to impute LDL-C values ~~based on the patients' baseline value.~~ ***in a model including placebo patients' data only***. Patients with missing LDL-C data at Week 12 who are still taking study treatment can be assumed to continue to benefit from study medication, and their missing value(s) can be assumed to be similar to those who remain on study treatment and have data. In this instance, it is reasonable to impute LDL-C values based on the observed values in their randomized treatment group at Week 12. ***Details for the PMM will be described in the SAP.***

To account for uncertainty, missing values will be imputed using multiple imputation. Imputed datasets will be analyzed using an ANCOVA model with the treatment and patient type (primary prevention; secondary prevention) as factors and baseline LDL-C as a covariate. Approximately ~~100~~ ***200*** imputed datasets will be created, with results from the analysis of each imputed dataset

combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

11.6 Secondary and Tertiary Endpoint Analysis

Secondary efficacy endpoints are also of interest for this study, in terms of controlling the overall Type I error rate, a gatekeeping or stepdown approach will be used to test the primary efficacy endpoint and then specific secondary efficacy endpoints sequentially in order to preserve the study-wise Type I error rate. The sequence for the stepdown procedure in this study is as follows:

1. Test the primary efficacy endpoint: percent change from baseline to Week 12 in LDL-C
2. Test the percent change from baseline to Week 24 in LDL-C
3. Test the percent change from baseline to Week 12 in non-HDL-C
4. Test the percent change from baseline to Week 12 in TC
5. Test the percent change from baseline to Week 12 in apoB
6. Test the percent change from baseline to Week 12 in hs-CRP

In this hierarchical testing structure, each hypothesis is tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. If the primary endpoint meets the criteria for statistical significance, then the percent change from baseline to Week 24 in LDL-C will be tested; and so forth.

For the remaining secondary efficacy endpoints and the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints, the p-values for those endpoints will be considered descriptive.

In general, change or percent change in lipid parameters at a given time point will be analyzed using similar ANCOVA model for the primary endpoint with treatment group ~~Percent change from baseline to Week 24 in LDL-C; change from baseline to Weeks 12 and 24 in LDL-C; percent change from baseline to Weeks 12 [redacted] in [redacted] non-HDL-C, [redacted] and TC; and percent change from baseline to Weeks 12and 24 in apoB and hs-CRP will each be analyzed using ANCOVA with treatment group~~ and patient type (primary prevention; secondary prevention) as factors and the relevant baseline as a covariate.

Baseline for [redacted] non-HDL-C, [redacted] and TC is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value.

Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. ***Same imputation method described for the primary endpoint will be used for those secondary endpoints included in the step-down procedure, while only observed data analysis will be used for other secondary and tertiary endpoints.*** ~~Only observed case data will be included in each analysis (no imputation will be performed for missing data).~~ For each lipid parameter and analysis time point, the LSM and

SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

~~For all continuous efficacy endpoints (percent change from baseline in LDL-C, HDL-C, non-[redacted]TC, [redacted]apoB, and hs-CRP; change from baseline in LDL-C; to Week 12 and 24, as appropriate), t~~***T***he ANCOVA assumption of normality will be assessed. If ***severe*** non-normality of the data is found at any time point for any parameter, either the data will be transformed so that it is normally distributed or a nonparametric test will be ~~used~~ ***considered*** instead of the planned ANCOVA.

Finally, the number and percent of patients in each treatment group requiring additional (post-randomization) TG-lowering therapy will be summarized. The medications will be summarized by treatment group.

11.7 Safety Analysis

~~No statistical analyses will be performed on any of the safety data in this study.~~

The summarization of AEs will include TEAEs, defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not related to the product. TEAEs and SAEs will be summarized by SOC, severity, and relationship to study drug for each treatment group. These AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates. Deaths, withdrawal from study treatment due to AEs, and withdrawal from the study due to AEs will each be summarized by treatment group.

CHANGE 32 PHARMACOKINETIC SAMPLE REVISION

Location:

Section 2, Synopsis; Section 11.8, Pharmacokinetics

Original Text:

Four plasma PK samples for analysis will be collected. Plasma concentrations of bempedoic acid and optionally, one or more of its metabolites, will be determined in patients who are receiving bempedoic acid. All patients, site personnel, and study personnel will remain blinded to treatment assignment throughout the duration of the study. Personnel performing the bioanalytical analysis of bempedoic acid concentrations will be unblinded in order to assay the appropriate samples during the study. Plasma concentrations of bempedoic acid and any measured metabolite will be included in the listings, but population PK analysis will be reported separately will be descriptive by time point.

New Text:

~~Four~~***Three*** plasma PK samples for analysis will be collected. Plasma concentrations of bempedoic acid and optionally, one or more of its metabolites, will be determined in patients who are receiving bempedoic acid. All patients, site personnel, and study personnel will remain blinded to treatment assignment throughout the duration of the study. Personnel performing the bioanalytical analysis of bempedoic acid concentrations will be unblinded in order to assay the

appropriate samples during the study. Plasma concentrations of bempedoic acid and any measured metabolite will be included in the listings, but population PK analysis will be reported separately will be descriptive by time point.

CHANGE 33 INFORMED CONSENT REVISION

Location:

Section 14.3, Written Informed Consent

Original Text:

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

A separate informed consent will be obtained for collecting the genetic blood sample.

The Principal Investigator(s) must maintain the original, signed ICD. A copy of the signed ICD must be given to the patient.

New Text:

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

~~A separate informed consent will be obtained for collecting the genetic blood sample.~~

The Principal Investigator(s) must maintain the original, signed ICD. A copy of the signed ICD must be given to the patient.

CHANGE 34 CASE REPORT FORM COLLECTION REVISION

Location:

Section 15.3, Case Report Forms and Study Records

Original Text:

It is essential that all dates appearing on the Sponsor's patient data collection forms for laboratory tests, cultures, etc, be the dates on which the specimens were obtained or the procedures performed. The eCRFs will be electronically signed by the Investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed within 48 hours following the evaluation.

New Text:

It is essential that all dates appearing on the Sponsor's patient data collection forms for laboratory tests, cultures, etc, be the dates on which the specimens were obtained or the procedures performed. The eCRFs will be electronically signed by the Investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed ***a timely manner according to the CRF completion guidelines.***~~within 48 hours following the evaluation.~~

CHANGE 35 STUDY ADMINISTRATIVE STRUCTURE REVISION

Location:

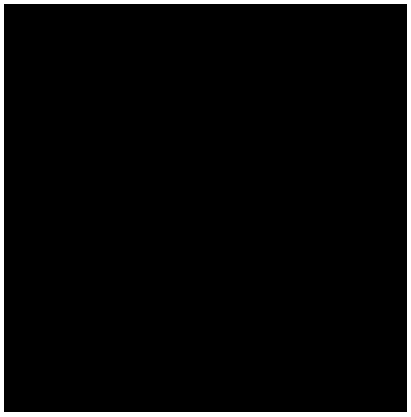
Section 16.2, Study Administrative Structure

Original Text:

Fill/Finish Manufacturing:

And

Secondary Packaging/Depot for Clinical Site Drug Shipments:

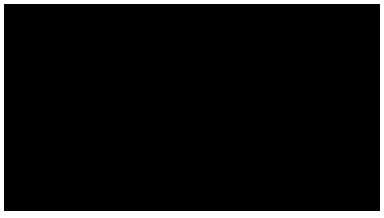


New Text:

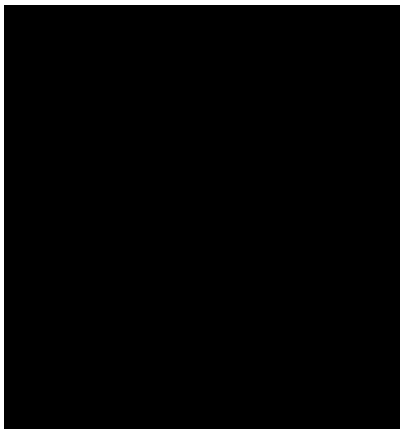
Investigational medicinal product supply chain details can be found in the pharmacy manual.

~~Fill/Finish Manufacturing:~~

~~And~~



~~Secondary Packaging/Depot for Clinical Site Drug Shipments:~~



CHANGE 36 SCHEDULE OF EVENTS REVISIONS

Location:

Appendix 1, Schedule of Events

Original Text:

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day -63 to -29**	**Day -28±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
Statin Intolerance Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight[4]	X			X			X	X
Height/BMI	X							
12-Lead ECG[5]			X					X
Vital Signs[6]	X	X	X	X	X		X	X
Serology[7]	X							
Serum Pregnancy/FSH[8]	X							
Urine Pregnancy[9]				X				
TSH	X							
Clinical Safety Labs[10]	X		X	X	X		X	X
Basic Fasting Lipids[11]	X		X	X	X		X	X
HbA_{1C}	X			X			X	X
10-mL reserve sample				X				X
PK Sample				X	X		X	X
Pharmacogenomics Sample (optional)				X				
apoB				X			X	X
hs-CRP				X			X	X
Diet and exercise counseling[12]	X	X	X	X	X	X	X	
Establish Patient Eligibility		X		X				
Randomization				X				
IWRS Contact[12]	X	X		X			X	X
Single-blind Drug Dispensing		X						
Double-blind Drug Dispensing				X			X	
Drug Return/Compliance			X	X	X		X	X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visits, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T5 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

[1] An optional basic fasting (minimum of 10 hours) lipid MAY be completed at Visit S2 (prior to starting single-blind medication) if patient fails to meet lipid entry criterion at Visit S1. If this optional basic fasting lipid is completed, the mean of the first value and the repeat value will be used to determine eligibility.

[2] A recheck of blood pressure may be completed at Visit S2 if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (diastolic blood pressure [DBP] and/or systolic blood pressure [SBP]) do not meet exclusionary values. Repeat labs may be completed at Visit S2 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

[4] Body weight will be measured while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[5] Single 12-lead ECG will be performed prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

[7] Serology for HBsAg, HCV-ABVivi.

[8] Pregnancy test completed in women of child-bearing potential only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

[9] Urine pregnancy test completed in women of child-bearing potential only just prior to randomization.

[10] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. A coagulation panel will be completed for all patients at Week -5 (Visit S1). A coagulation panel will be completed only for patients on anti-coagulant therapy at Day 1 (Visit T1) and 3 to 5 days later. Please refer to laboratory manual for detailed schedule of tests.

[11] Basic fasting (minimum of 10 hours) lipids include total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

[12] Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

[13] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

New Text:

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Visit	**S1**[1,2]	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5/EOS**[3]
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**
Procedure	**Day ~~-35~~± ~~7~~ ~~63 to 29~~**	**Day -28±3**	**Day -7±3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**
Informed Consent	X							
Enrollment Criteria	X							
Demographics	X							
Medical History	X							
Statin Intolerance Status Determination	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X
Physical Exam		X						X
Weight[4]	X			X			X	X
Height/BMI	X							
12-Lead ECG[5]			X					X
Vital Signs[6]	X	X	X	X	X		X	X
Serology[7]	X							
Serum Pregnancy/FSH[8]	X							
Urine Pregnancy[9]				X				
TSH	X							
Clinical Safety Labs[10]	X		X	X	X		X	X
Basic Fasting Lipids[11]	X		X	X	X		X	X
HbA_{1C}	X			X			X	X
~~10 mL reserve sample~~				~~X~~				~~X~~
PK Sample				~~X~~	X		X	X
~~Pharmacogenomics Sample (optional)~~				~~X~~				
apoB				X			X	X
hs-CRP				X			X	X
Diet and exercise counseling[12]	X	X	X	X	X	X	X	
Establish Patient Eligibility		X		X				
Randomization				X				
IWRS Contact[~~12~~ 13]	X	X		X			X	X
Single-blind Drug Dispensing		X						
Double-blind Drug Dispensing				X			X	
Drug Return/Compliance			X	X	X		X	X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visits, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). ~~For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T5 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.~~

[1] An optional ~~basic~~ fasting (minimum of 10 hours) ~~lipid~~ ***TG assessment*** MAY be completed ***between Visit S1 and*** ~~at~~ Visit S2 (prior to starting single-blind medication) if patient fails to meet ~~lipid~~ ***TG*** entry criterion at Visit S1. If this optional ~~basic fasting lipid~~ ***TG*** is completed, the ~~mean of the first value and the~~ repeat value will be used to determine eligibility.

[2] A recheck of blood pressure may be completed ***between Visit S1 and*** ~~at~~ Visit S2 if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (diastolic blood pressure [DBP] and/or systolic blood pressure [SBP]) do not meet exclusionary values. Repeat labs may be completed at Visit S2 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

[4] Body weight will be measured while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[5] Single 12-lead ECG will be performed prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

[7] Serology for HBsAg, HCV-ABVivi.

[8] Pregnancy test completed in women of child-bearing potential only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

[9] Urine pregnancy test completed in women of child-bearing potential only just prior to randomization.

[10] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. A coagulation panel will be completed for all patients at Week -5 (Visit S1). A coagulation panel will be completed only for patients on anti-coagulant therapy at Day 1 (Visit T1) and 3 to 5 days later. ***For these visits, the sample may be analyzed at either the central or a local lab.*** Please refer to laboratory manual for detailed schedule of tests.

[11] Basic fasting (minimum of 10 hours) lipids include total cholesterol, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides. ~~Repeat within 1 week if exceed protocol-specified criteria.~~

[12] Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

[13] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

CHANGE 37 REMOVAL OF DATE WITHIN THE BODY OF APPENDIX 2 PAGES

Location:

Appendix 2: Final Date, all pages within Appendix 2

Original text:

Final Date: 25 August 2016

New text:

~~**Final Date:** 25 August 2016~~

CHANGE 38 SPONSOR'S SIGNATORY CHANGES

Location:

Appendix 2, Sponsor's Signature

Original Text:

Signed: _____ Date: _____

[redacted]

New Text:

Signed: _____ Date: _____

[redacted]

Original Text:

Signed: _____ Date: _____

[redacted]

New Text:

Signed: _____ Date: _____

[redacted]