



BEMPEDOIC ACID

1002-048

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED,
PARALLEL GROUP, MULTICENTER STUDY TO EVALUATE THE
EFFICACY AND SAFETY OF BEMPEDOIC ACID (ETC-1002)
180 MG/DAY AS ADD-ON TO EZETIMIBE THERAPY IN PATIENTS
WITH ELEVATED LDL-C ON LOW DOSE OR LESS THAN LOW DOSE
STATINS**

Study Phase: 3
IND Number: 106654
Indication: Treatment of hyperlipidemia
Investigators: Approximately 75 sites in North America and Europe
Sponsor: Esperion Therapeutics, Inc.
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Ann Arbor, MI 48108
[REDACTED]

EudraCT: 2016-004084-39

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Confidentiality Statement

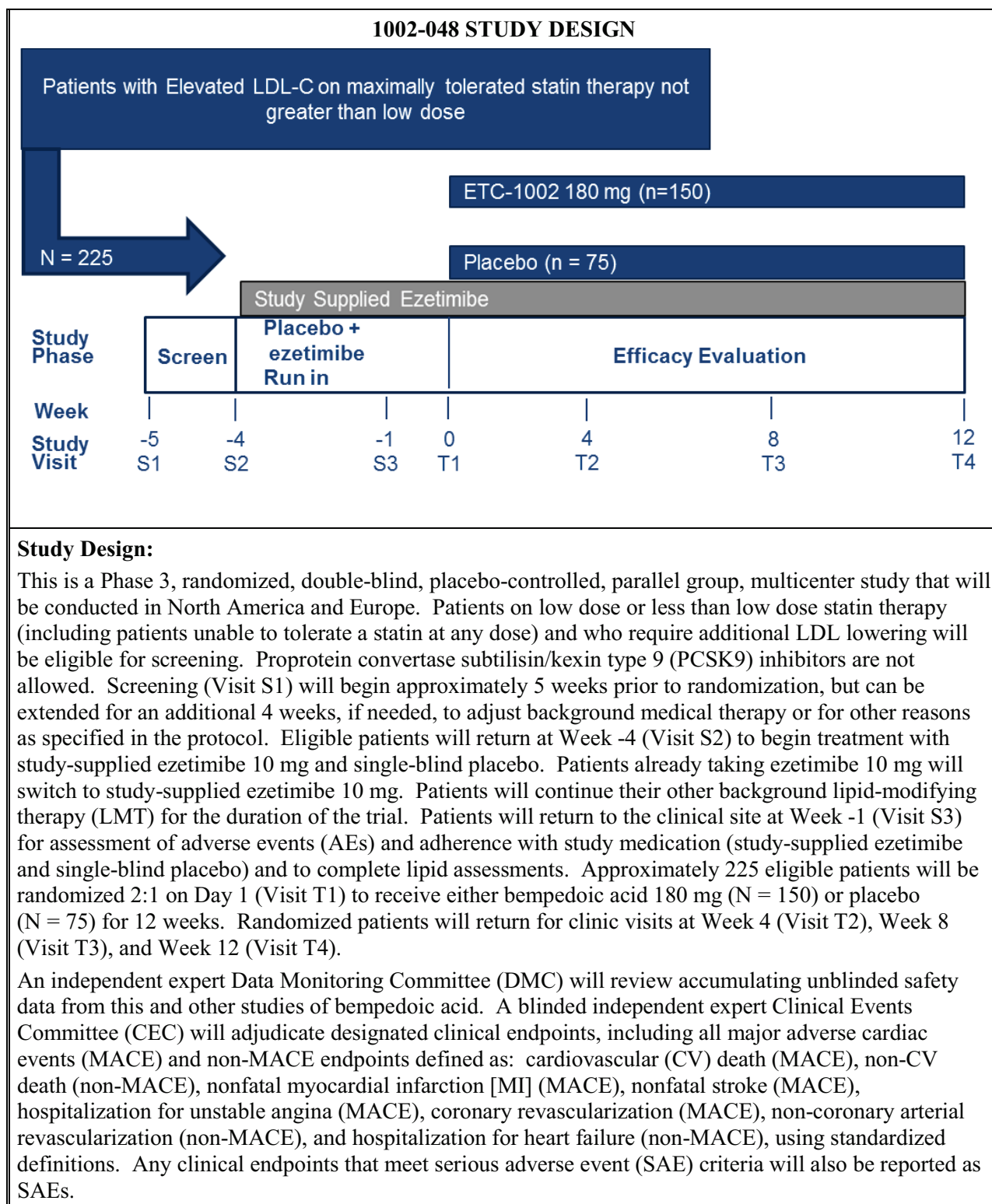
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2. SYNOPSIS

Name of Sponsor/Company: Esperion Therapeutics, Inc.
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C On Low Dose or Less Than Low Dose Statins
Study Number: 1002-048
Study Phase: 3
Objectives: Primary: <ul style="list-style-type: none">• To assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing low-density lipoprotein cholesterol (LDL-C) when added to ezetimibe therapy in patients with elevated LDL-C Secondary: <ul style="list-style-type: none">• To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on<ul style="list-style-type: none">– non-high-density lipoprotein cholesterol (non-HDL-C),– total cholesterol (TC),– apolipoprotein B (apoB), and– high-sensitivity C-reactive protein (hs-CRP)• To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) when added to ezetimibe• To evaluate 12-week safety and tolerability of bempedoic acid 180 mg/day compared with placebo when added to ezetimibe Tertiary: <ul style="list-style-type: none">• To evaluate the effects of treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy at 4 and 8 weeks on the following parameters:<ul style="list-style-type: none">– LDL-C– Non-HDL-C– TC– TG– HDL-C



Study Endpoints:Primary efficacy endpoint:

- Percent change from baseline to Week 12 in LDL-C

Secondary efficacy endpoints (specific to stepdown approach):

1. Percent change from baseline to Week 12 in:
 - a. non-HDL-C
 - b. TC
 - c. apoB
 - d. hs-CRP

Other secondary efficacy endpoints:

2. Percent change from baseline to Week 12 in:
 - a. TG
 - b. HDL-C

Tertiary efficacy endpoints:

1. Assessments of percent change from baseline in lipid levels at the additional time points of Week 4 (T2) and Week 8 (T3) in:
 - a. LDL-C
 - b. Non-HDL-C
 - c. TC
 - d. TG
 - e. HDL-C
2. Assessments of absolute change from baseline to Weeks 4, 8, and 12 in LDL-C

Safety Endpoints:

- a. Subject incidence to treatment-emergent adverse events (TEAE)
- b. Safety laboratory values and vital signs
- c. Electrocardiogram (ECG) findings
- d. Cardiovascular event rates

Study Population:

Approximately 225 male and female patients.

Inclusion Criteria:

Each potential patient must satisfy all inclusion criteria to be enrolled in the study. Selected inclusion criteria are listed below; all inclusion criteria are listed in the protocol body.

1. Provision of written informed consent prior to any study-specific procedure
2. Age ≥ 18 years or legal age of majority based on regional law, whichever is greater, at Week -5 (Visit S1)
3. Fasting (minimum of 10 hours) calculated LDL-C at Week -5 (Visit S1) as defined by ezetimibe use at screening:
 - For patients who have been taking ezetimibe 10 mg daily prior to Week -5 (Visit S1): Fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) on stable background LMT (greater than or equal to 4 weeks prior to screening)
 - For patients who have not been taking ezetimibe prior to Week -5 (Visit S1): Fasting LDL-C

<p>≥120 mg/dL (3.1 mmol/L) on stable background LMT (greater than or equal to 4 weeks prior to screening).</p> <ul style="list-style-type: none">• All patients must have fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3). <p>4. Currently receiving stable (greater than or equal to 4 weeks prior to screening) background statin dose that does not exceed low dose statin therapy.</p> <p>Note: Patients must report attempting statin therapy and being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered.</p> <p>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.</p> <p>Very 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.</p> <p>Patients on low or very low dose statin or unable to tolerate any statin at any dose are eligible. Patients may continue taking low or very low dose statin therapy throughout the study provided that it is stable (greater than or equal to 4 weeks) and well tolerated. Patients unable to take any dose of statins are also eligible provided that statin therapy has been attempted.</p> <p>5. Men and nonpregnant, nonlactating women. Women must be either</p> <ul style="list-style-type: none">• Naturally postmenopausal defined as ≥1 year without menses and<ul style="list-style-type: none">– ≥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 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:<ul style="list-style-type: none">– oral, implantable, injectable, or topical 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). <p>Note: There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.</p>	<p>Exclusion Criteria:</p> <p>Patients who meet any of the exclusion criteria are not eligible. Selected exclusion criteria are listed below; all exclusion criteria are listed in the protocol body.</p> <ol style="list-style-type: none">1. Body mass index (BMI) >50 kg/m²2. Recent history of documented clinically significant cardiovascular disease including, but not limited to<ul style="list-style-type: none">• Within 3 months of screening (Week -5 [Visit S1]) or between screening and randomization
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- visits: MI, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease.
- Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥ 160 mm Hg and diastolic blood pressure (DBP) ≥ 100 mm Hg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the investigator, the screening period may be extended up to 4 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria
 - Within 3 months of screening [Week -5 (Visit S1)] or between screening and randomization visits, an arrhythmia requiring medical intervention.
 - Planned revascularization procedures
 - New York Heart Association (NYHA) Class IV heart failure
3. Total fasting (minimum of 10 hours) TG ≥ 500 mg/dL (5.6 mmol/L) at Week -5 (S1)
Note: TG may be repeated 1 time with the screening period extended up to 4 weeks. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.
4. Hemoglobin A_{1c} (HbA_{1c}) $\geq 10\%$ at Week -5 (Visit S1)
5. Persistent poor adherence with study-supplied ezetimibe and/or single-blind, placebo study drug (ie, ingesting $<80\%$ of planned doses) or lack of tolerance to run-in medications assessed prior to randomization.
6. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $>1.5 \times$ 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.
7. Liver disease or dysfunction, including:
- Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -4 (Visit S2), or
 - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) $\geq 2 \times$ ULN, and/or total bilirubin (TB) $\geq 2 \times$ ULN at Week -5 (Visit S1). If TB $\geq 1.2 \times$ 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 and/or AST 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, the patient can be enrolled.
8. Renal dysfunction or glomerulonephritis, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min at Week -5 (Visit S1). Note, a single repeat qualifying eGFR, performed at the discretion of the investigator, is acceptable;
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 <10.0 g/dL at Week -5 (Visit S1);
11. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ

- are allowed;
12. Unexplained creatine kinase (CK) $>3 \times \text{ULN}$ at any time prior to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times \text{ULN}$ prior to randomization;
 13. History of drug or alcohol abuse within the last 2 years or reported current consumption of >14 alcoholic drinks/week, or any illicit drug use, history of amphetamine and derivatives abuse or cocaine abuse. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator;
 14. Blood donation, participation in a multiple blood draws, clinical study, major trauma, blood transfusion or surgery with or without blood loss within 30 days prior to randomization;
 15. Use of any experimental or investigational drugs within 30 days prior to screening. Patients who have enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9 are excluded;
 16. Previous enrollment in a bempedoic acid clinical study.
 17. Use of any of the following drugs prior to screening (Week -5, Visit S1) or a plan to use these drugs during the study as follows. Screening can be extended for an additional 4 weeks if needed to adjust background therapy.
 - Within 2 weeks prior to screening
 - Cholestin or red yeast rice containing-products (also known as monascus purpureus extract)
 - Within 4 weeks prior to screening
 - Statin doses exceeding those defined as low dose. Doses exceeding low dose statin therapy are defined as an average daily dose of rosuvastatin greater than 5 mg, atorvastatin greater than 10 mg, simvastatin greater than 10 mg, lovastatin greater than 20 mg, pravastatin greater than 40 mg, fluvastatin greater than 40 mg, or pitavastatin greater than 2 mg.
 - Within 6 weeks prior to screening for patients taking a statin
 - Gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label
 - Within 3 months prior to screening:
 - Lomitapide or apheresis therapy
 - Probenecid or cyclosporine
 - Within 4 months prior to screening
 - PCSK9-inhibitors
 - Within 6 months prior to screening
 - Mipomersen
 - CETP inhibitors within the last 2 years to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months prior to screening (Week -5, Visit S1)
 18. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization (Day 1, Visit T1):
 - Hormone replacement (within 6 weeks prior to randomization)
 - Thyroid replacement (within 6 weeks prior to randomization)
 - Diabetes medications (within 4 weeks prior to randomization)
 - Obesity medication (within 4 weeks prior to randomization)
 19. 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.

20. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or any Sponsor personnel.
21. Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of study drug.
22. Previous intolerance to ezetimibe.

Investigational medicinal product(s) (IMP), dosage and mode of administration:

- Bempedoic acid 180-mg tablets.
- Matching placebo tablets
- All IMP will be ingested once daily (once every 24 hours, at approximately the same time each day) with or without food.

Non-investigational medicinal product(s) (NIMP), dosage and mode of administration:

Background lipid-lowering therapy:

- Study supplied ezetimibe 10 mg ingested once daily (every 24 hours, at approximately the same time each day when IMP is ingested) with or without food.
- All other background LMT will be ingested as prescribed by a physician

Criteria for evaluation:

Lipid and Cardiometabolic Assessments:

- Calculated LDL-C, HDL-C, non-HDL-C, TC, TG, and apoB.
 - 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.
- hs-CRP

Safety Assessments:

Adverse events and SAEs will be collected and reported. Clinical endpoints will be collected and adjudicated by an independent CEC. Clinical endpoints will also be reported as SAEs. 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, 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), International Normalized Ratio (INR)
- 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 (CO₂), 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:

HBsAg, hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), TSH

Pharmacokinetic (PK) and other Biomarkers:

- hs-CRP
- Plasma PK concentrations will be collected prior to dose at Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4) for use in further developing the population PK model.

Safety and Monitoring:

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.

Diabetes and Hyperglycemia:

Cases of new onset of diabetes will be recorded as AEs. Clinical laboratories, including HbA_{1C} and fasting 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 MACE and non-MACE cardiovascular AEs, SAEs, standard vital signs, and ECGs.

Further details on occurrence and monitoring of AESI 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.

The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group is expected to provide more than 95% power to detect a difference of 15% in the percent change from baseline to Week 12 in calculated LDL-C between the bempedoic acid treatment group and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15%. The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group gives a total study sample size of 225.

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 their actual treatment.

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.

Disposition 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.

Primary Efficacy 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 as a factor 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. Missing data will be imputed using multiple imputation method that accounts for treatment adherence via a pattern mixture model (PMM). Imputed datasets will be analyzed using ANCOVA with treatment as a factor 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 final results, 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 Analysis

Absolute and percent change from baseline to specific time points for lipid parameters and hs-CRP will each be analyzed similarly using ANCOVA with treatment group as a factor and the relevant baseline as the covariate. Baseline for non-HDL-C, HDL-C, TC, and TG are defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1), while 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. For each lipid parameter at each 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 and absolute change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP; to Weeks 4, 8, and 12, 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.

Safety Analyses

The summarization of AEs will include only 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, HbA_{1C}, fasting 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 postbaseline 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 criteria ($\geq 3 \times \text{ULN}$ for either ALT or AST, with accompanying TB $> 2 \times \text{ULN}$ in the absence of other known causes ($\geq 2 \times \text{ULN}$ conjugated [direct] bilirubin will be used

in patients with Gilbert's Disease), 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 and Hyperglycemia

Cases of worsening and 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.

PK and Other biomarkers

PK plasma concentrations for ETC-1002 and its metabolite ESP15228 will be summarized at Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4).

Clinical Labs:

Hematology:

Hct, Hgb, MCH, MCHC, MCV, platelet count, RBC count, WBC count with differential (absolute values only)

Urinalysis (Dipstick):

Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen

Urine pregnancy test (only for women of child bearing potential)

Urinalysis (Microscopic): Obtained centrally only if positive urine dipstick

Bacteria, casts, crystals, epithelial cells, RBC, WBC

Coagulation:

PT and INR

Serum Chemistry:

ALB, ALK-P, ALT (SGPT), AST (SGOT), TB, BUN, Ca, CO₂, Cl, creatinine, CK, fasting glucose, LDH, phosphorus, K, Na, total and direct bilirubin, total protein, uric acid, HbA_{1c}

Other Screening Labs:

HBsAg, HCV, serum pregnancy test (only for women of childbearing potential), FSH (only to confirm postmenopausal status in appropriate females), TSH

Basic Lipid Parameters:

TC, calculated LDL-C (or measured if necessary), HDL-C, TG

Special Lipid Parameters

apoB

Other Biomarkers and PK:

hs-CRP, PK samples of ETC-1002 and ESP15228.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACL	adenosine triphosphate-citrate lyase
ACS	acyl-CoA synthetase
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
apoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular diseases
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
CEC	Clinical Event Committee
CETP-I	Cholesteryl ester transfer protein inhibitor
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CK	creatinine kinase
Cl	chloride
C _{max}	time to peak maximum concentrations
CMV	cytomegalovirus
CNS	central nervous system
CoA	acetyl-coenzyme A
CO ₂	carbon dioxide
CRO	contract research organization

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
EOS	end of study
ETC-1002-CoA	ETC-1002-coenzyme A
EU	European Union
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
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-AB	hepatitis C antibodies
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
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
LPLV	last patient last visit
LMT	lipid-modifying therapy
LS	least square
LSM	least square mean
MACE	major adverse cardiac 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
NIMP	non-investigational medicinal product(s)
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	physical exam
PK	pharmacokinetic(s)
PG	pharmacogenomic
PMM	pattern mixed model
PT	prothrombin time
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SBP	systolic blood pressure
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
siRNA	small interfering ribonucleic acid
SOC	system organ class
SOP	standard operating procedures
SP	safety population
SUSARS	suspected and unexpected serious adverse reactions
$t_{1/2}$	terminal elimination half-live
T2DM	type 2 diabetes mellitus
TB	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglycerides
TSH	thyroid-stimulating hormone
TQT	thorough QT/QTc
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1. Lipid-Regulating Drugs and Cardiovascular Disease

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 (CV) risk unable to meet their treatment goals with currently available lipid-lowering therapies.

The target population for this study includes patients with elevated LDL-C who are only able to tolerate low dose or less than low dose of statins (including those not taking a statin due to inability to tolerate a statin) or in combination with other lipid-modifying therapies (in some cases also includes ezetimibe) and who require additional LDL-C lowering.

Elevated LDL-C is a major modifiable risk factor for the development of atherosclerosis and atherosclerotic cardiovascular diseases (ASCVD) [1]. Despite aggressive interventional and pharmacologic therapies, CV disease is the number 1 cause of death globally [2]. An estimated 17.5 million people died from CV diseases in 2012, representing 31% of all deaths worldwide. Of these deaths, an estimated 7.4 million were due to coronary heart disease (CHD) and 6.7 million were due to stroke [2]. Cardiovascular disease remains the leading cause of death among Americans, Europeans, and around the world. The Global Burden of Disease study estimated that 29.6% of all deaths (approximately 15.6 million deaths) were caused by CV disease in 2010, more than all communicable, maternal, neonatal, and nutritional disorders combined, and double the number of deaths caused by cancers [3]. In the United States (US), based on 2011 death rate data, more than 2150 Americans die from CV diseases daily, an average of 1 death every 40 seconds. Approximately 155,000 Americans dying from CV disease are less than 65 years of age. In 2011, 34% of deaths due to CV disease occurred prior to the age of 75 years, less than the current 78.7-year average life expectancy [4].

LDL-C is largely accepted as a valid surrogate endpoint of CV events by clinicians and regulatory authorities [5]. Long-term elevations in LDL-C lead to progressive accumulation of atherosclerotic lesions in the walls of arteries that require long-term management. While lifestyle changes are the primary intervention, these measures rarely decrease plasma LDL-C by >15%. Evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, genetic variants (both gain of function and loss of function). Large randomized clinical studies aimed at lowering LDL-C show a consistent log-linear relationship between LDL-C reduction and CV risk reduction, independent of the way LDL-C lowering was achieved based on mechanism of action [6,7,8,9]. A published patient-level meta-analysis including 26 trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes [7]. This analysis showed that a 1 mmol/L reduction in LDL-C was associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. Intensive statin therapy relative to low/moderate intensity statin treatment produces greater benefit in patients at high CV risk [10].

Unfortunately, some patients with elevated LDL-C are unable to take high intensity statins due to dosing limits based on comorbidities, contraindications, and/or tolerance [11]. Nonstatin therapies may provide additional lowering of CV risk as demonstrated in the IMPROVE-IT trial which added ezetimibe to statin therapy [12]. The addition of bempedoic acid to ezetimibe and low intensity statin therapy may offer additional lowering of LDL-C with associated lowering of CV risk. Bempedoic acid has been well tolerated to date and Phase 2 data demonstrate significant LDL-C lowering, prompting further evaluation in Phase 3 clinical studies.

4.2. Background on 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 the liver leading to increased low-density lipoprotein receptor (LDLR) expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002-CoA decreases 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. Nonclinical Experience

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2.3. Previous Human Experience

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2.4. Dose Selection

[REDACTED]

4.2.5. Background Therapy

In this study, bempedoic acid is being evaluated as an add-on therapy to ezetimibe for decreasing LDL-C in addition to background low dose or less than low dose statin therapy in patients with elevated LDL-C who require additional LDL-C lowering.

4.2.6. Risk Benefit Summary

To date, the nonclinical and clinical data indicate that bempedoic acid has a favorable risk-benefit profile. The ability of bempedoic acid to achieve clinically meaningful LDL-C-lowering responses while demonstrating a favorable tolerability profile in a variety of patient populations supports continued development of bempedoic acid, an oral ACL inhibitor, in the Phase 3 program.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The primary objective of this study is

- To assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing LDL-C when added to ezetimibe therapy in patients with elevated LDL-C

5.2. Secondary Objectives

The secondary objectives of this study are

- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on
 - non-high-density lipoprotein cholesterol (non-HDL-C),
 - total cholesterol (TC),
 - apolipoprotein B (apoB), and
 - high-sensitivity C-reactive protein (hs-CRP)
- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo on TG and HDL-C when added to ezetimibe
- To evaluate 12-week safety and tolerability of bempedoic acid 180 mg/day compared with placebo when added to ezetimibe

5.3. Tertiary Objectives

The tertiary objectives of this study are

- To evaluate the effects of treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy at Weeks 4 and 8 on:
 - LDL-C
 - Non-HDL-C
 - TC
 - TG
 - HDL-C

5.4. Study Endpoints

5.4.1. Primary Efficacy Endpoint

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

5.4.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints (specific to stepdown approach [[Section 12.6](#)]) are

1. Percent change from baseline to Week 12 in
 - a. non-HDL-C
 - b. TC
 - c. apoB
 - d. hs-CRP

Other secondary efficacy endpoints are

2. Percent change from baseline to Week 12 in
 - a. TG
 - b. HDL-C

5.4.3. Tertiary Efficacy Endpoints

Tertiary endpoints include assessments of percent change and absolute change from baseline in lipid levels at the additional time points of Week 4 (T2) and Week 8 (T3).

1. Percent change from baseline to Weeks 4 and 8 in
 - a. LDL-C
 - b. Non-HDL-C
 - c. TC
 - d. TG
 - e. HDL-C
2. Absolute change from baseline to Weeks 4, 8, and 12 in LDL-C.

5.4.4. Safety Endpoints

- a. Subject incidence to TEAE
- b. Safety laboratory values and vital signs
- c. ECG findings
- d. Cardiovascular event rates

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of bempedoic acid as an add-on therapy to ezetimibe in patients with elevated LDL-C.

Screening Week -5 (Visit S1) will begin 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 as specified in the protocol. Eligible patients will return to the clinical site at Week -4 (Visit S2) to begin treatment with study supplied ezetimibe 10 mg and single-blind placebo. Patients having their own supply of ezetimibe will switch to study-supplied ezetimibe at this visit.

6.2. Study Hypothesis

The study will assess the 12-week efficacy of bempedoic acid as an add-on therapy to ezetimibe in decreasing LDL-C versus placebo. The treatment duration of 12 weeks and study population of 225 patients will provide data on the lipid profile, safety, and tolerability of bempedoic acid in patients with elevated LDL-C who have a need for additional lipid-lowering therapy.

6.3. Study Duration and Period

The expected total duration of study participation for each randomized patient is approximately 17 weeks. The study will consist of an approximately 1-week screening period, a 4-week placebo run-in period, and a 12-week of treatment period.

6.4. End of Study

The study will end when the last randomized patient completes the Week 12 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 11 months.

6.5. Number of Patients

Approximately 225 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (N = 150) or placebo (N = 75) for 12 weeks.

6.6. Patient Identification Numbers

A unique patient identification number will be assigned to identify each patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, their patient identification number cannot be assigned to another patient.

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

6.6.1. Screening and Placebo Run-in Period

Screening will occur approximately 5 weeks prior to Day 1 (Visit T1) when the patient's eligibility will be evaluated. Eligible patients who are taking concomitant medications must be on stable regimens as defined in [Section 7.1](#). At the investigator's discretion, screening may 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 open label ezetimibe and single-blind placebo. Eligible patients will return at Week -1 (Visit S3) for basic fasting lipids assessments and an assessment of tolerability and study drug adherence (see [Section 7](#) for eligibility criteria). 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 fails screening prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of AEs.

6.6.2. Randomization and Treatment Periods

For patients who satisfy all entry criteria and complete the 1-week screening period and 4-week run-in period, randomization to a treatment group will occur via IWRS at Week 0 (Visit T1). Approximately 225 patients will be randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- Bempedoic acid 180-mg tablet
- Matching placebo tablet

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Subject Inclusion Criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study.

1. Provision of written informed consent prior to any study-specific procedure
2. Age ≥ 18 years or legal age of majority based on regional law, whichever is greater, at Week -5 (Visit S1)
3. Fasting (minimum of 10 hours) calculated LDL-C at Week -5 (Visit S1) as defined by ezetimibe use at screening:
 - For patients who have been taking ezetimibe 10 mg daily prior to Week -5 (Visit S1): Fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) on stable background lipid-modifying therapy (LMT; greater than or equal to 4 weeks prior to screening)
 - For patients who have not been taking ezetimibe Week -5 (Visit S1): Fasting LDL-C ≥ 120 mg/dL (3.1 mmol/L) on stable background LMT (greater than or equal to 4 weeks prior to screening).
 - All patients must have fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3)
4. Currently receiving stable (greater than or equal to 4 weeks prior to screening) background statin dose that does not exceed low dose statin therapy. Patients must report attempting statin therapy and being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered.

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.

Very 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.

Patients on low or very low dose statin or unable to tolerate any statin at any dose are eligible. Patients may continue taking low or very low dose statin therapy throughout the study provided that it is stable (greater than or equal to 4 weeks) and well tolerated. Patients unable to take any dose of statins are also eligible provided that statin therapy has been attempted as described above.
5. 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 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, implantable, injectable, or topical 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).

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

7.2. Subject Exclusion Criteria

Patients who meet any of the following criteria are not eligible:

1. Body mass index (BMI) $>50 \text{ kg/m}^2$
2. Recent history of documented clinically significant cardiovascular disease including, but not limited to
 - Within 3 months of screening (Week -5 [Visit S1]) or between screening and randomization, myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease
 - Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) $\geq 160 \text{ mm Hg}$ and diastolic blood pressure (DBP) $\geq 100 \text{ mm Hg}$ after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the investigator, the screening period may be extended up to 4 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria
 - Within 3 months of screening (Week -5 [Visit S1]) or between screening and randomization visits, arrhythmia requiring medical intervention.

- Planned revascularization procedures
 - New York Heart Association (NYHA) Class IV heart failure
3. Total fasting (minimum of 10 hours) TG ≥ 500 mg/dL (5.6 mmol/L) at Week -5 (Visit S1)
- Note: TG may be repeated 1 time with the screening period extended up to 4 weeks. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.
4. Glycosylated hemoglobin, Type A_{1C} (HbA_{1C}) $\geq 10\%$ at Week -5 (Visit S1)
5. Persistent poor adherence with study-supplied ezetimibe and/or single-blind placebo study drug (ie, ingesting $<80\%$ of planned doses) or lack of tolerance to run-in medications assessed prior to randomization.
6. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $>1.5 \times$ the upper limit of normal (ULN) at Week -5 (Visit S1);
7. Liver disease or dysfunction, including:
- Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -4 (Visit S2), or
 - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\geq 2.0 \times$ ULN at Week -5 (Visit S1). If total bilirubin (TB) $\geq 1.2 \times$ 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 and/or AST 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, the patient can be enrolled.
8. Renal dysfunction or glomerulonephritis, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min at Week -5 (Visit S1). Note, a single repeat qualifying eGFR, performed at the discretion of the investigator, is acceptable;
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 <10.0 g/dL at Week -5 (Visit S1);
11. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed
12. Unexplained creatine kinase (CK) $>3 \times$ ULN at any time prior to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK $\leq 3 \times$ ULN prior to randomization;

13. History of drug or alcohol abuse within the last 2 years or reported current consumption of >14 alcoholic drinks/week, or any illicit drug use, history of amphetamine and derivatives abuse or cocaine abuse. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator;
14. Blood donation, participation in a multiple blood draws, clinical study, major trauma, blood transfusion or surgery with or without blood loss within 30 days prior to randomization;
15. Use of any experimental or investigational drugs within 30 days prior to screening. Patients who have enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9 are excluded;
16. Previous enrollment in a bempedoic acid clinical study.
17. Use of any of the following drugs prior to screening (Week -5, Visit S1) or a plan to use these drugs during the study as follows:
 - Within 2 weeks prior to screening
 - Cholestin or red yeast rice-containing products (also known as monascus purpureus extract)
 - Within 4 weeks prior to screening
 - Statin doses exceeding those defined as low dose. Doses exceeding low dose statin therapy are defined as an average daily dose of rosuvastatin greater than 5 mg, atorvastatin greater than 10 mg, simvastatin greater than 10 mg, lovastatin greater than 20 mg, pravastatin greater than 40 mg, fluvastatin greater than 40 mg, or pitavastatin greater than 2 mg.
 - Within 6 weeks prior to screening for patients taking a statin
 - Gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label
 - Within 3 months prior to screening:
 - Lomitapide or apheresis therapy
 - Probenecid or cyclosporine
 - Within 4 months prior to screening
 - Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
 - Within 6 months prior to screening
 - Mipomersen
 - Cholesteryl ester transfer protein inhibitor (CETP-I) within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months to screening (Week -5, Visit S1)

18. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:

- Hormone replacement (within 6 weeks prior to randomization)
- Thyroid replacement (within 6 weeks prior to randomization)
- Diabetes medications (within 4 weeks prior to randomization)
- Obesity medication (4 weeks prior to randomization)

19. 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.

20. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or Sponsor.

21. Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of study drug.

22. Previous intolerance to ezetimibe.

7.3. 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.

7.4. Investigator/Sponsor Suspension or Termination of Patient Enrollment

If, in the opinion of the investigator, the clinical observations in the study suggest that it may be unwise to continue, the investigator may suspend or terminate the study at his/her site after consultation with the Sponsor (or designee). A written statement fully documenting the reasons for such a termination will be provided to the Sponsor (or designee) and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The Sponsor has the right to terminate the study or to close a site and remove all study materials from the clinical site. A written statement will be provided to the investigator, the IRB or IEC, and regulatory authorities, if required.

Possible reasons for termination of the study at a clinical site 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.

8. TREATMENT OF PATIENTS

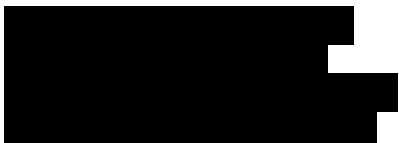
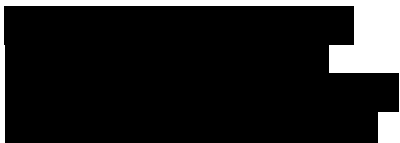
8.1. IMP Dosage and Mode of Administration

During the double-blind treatment period, patients will ingest once daily (once every 24 hours at approximately the same time each day) with or without food either

- Bempedoic acid 180-mg tablets, or
- Matching placebo tablets

8.2. Description of Investigational Medicinal Product

Table 2: Investigational Medicinal Products

	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, childproof cap	35- and/or 100-count bottle (depending on visit) with screw-on, childproof cap ^a
Route of Administration:	Oral, daily, with or without food	Oral, daily, with or without food
Physical Description:		

^a A 100-day supply of IMP will be included in the 100-count bottle and a 35-day supply of single blind placebo lead-in will be included in the 35-count bottle.

Please see Pharmacy Manual for detailed storage requirements and instructions.

8.3. Non-investigational Medicine Products Dose and Description

8.3.1. Ezetimibe

Eligible patients will begin single-blind treatment with study-supplied and labeled ezetimibe 10 mg and placebo at Week -4 (Visit S2). Treatment with study-supplied ezetimibe 10 mg will continue after double-blind randomization through Week 12/end of study (EOS) (Visit T4).

Please see Pharmacy Manual for detailed storage requirements and instructions.

8.3.2. Background Lipid-Lowering Therapy

All other background lipid-lowering therapy will be ingested as prescribed by a physician

8.4. Concomitant Medications

8.4.1. Lipid-Regulating Medications and Supplements

Eligible patients will be those currently receiving stable (greater than or equal to 4 weeks prior to screening, Week -5, Visit S1) background statin therapy that does not exceed low dose. 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. Very 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. Patients unable to take any dose of statins are also eligible provided that statin therapy has been attempted as described above.

Patients should continue taking their LMT throughout the study.

PCSK9 inhibitors are not allowed during the study period.

The ezetimibe and IMP will be study-supplied. Patients on ezetimibe at Visit S1 will stop taking their supply of medication at Visit S2 and begin taking study-supplied ezetimibe.

8.4.2. Prohibited Medications

Patients should not use the following medications (monotherapies or combination therapies) prior to screening as defined in the exclusion criteria and below, or at any time during the study.

- Within 2 weeks prior to screening, Week -5, Visit S1:
 - Cholestin or red yeast rice-containing products (also known as monascus purpureus extract)
- Within 4 weeks prior to screening, Week -5, Visit S1:
 - Statin dose exceeding low dose as defined under inclusion criteria.
 - New or planned dose changes of systemic corticosteroids
- Within 6 weeks prior to screening, Week -5, Visit S1 for patients taking a statin:
 - Gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label
- Within 3 months prior to screening, Week -5, Visit S1:
 - Lomitapide or apheresis therapy
 - Probenecid or cyclosporine
- PCSK9-inhibitors within 4 months prior to screening, Week -5, Visit S1
- Mipomersen within 6 months prior to screening, Week -5, Visit S1
- CETP-inhibitors within the last 2 years before screening, Week -5, Visit S1 except for evaceptrapib within the last 3 months prior 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 before screening (Week -5, Visit S1). Patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9 are excluded.

8.4.3. Allowable Medications

LMT not prohibited are allowed and should remain stable for at least 4 weeks prior to screening (Week -5, Visit S1); fibrates (with the exception of gemfibrozil which is exclusionary in patients taking a statin) should remain stable for at least 6 weeks prior to screening (Week -5, Visit S1). Use of any of the following medications are allowed if started before the randomization visit (Day 1, Visit T1) as defined below and are expected to remain stable through completion of the study:

- Hormone replacement therapy (≥ 6 weeks before Day 1, Visit T1)
- Thyroid replacement therapy (≥ 6 weeks before Day 1, Visit T1)
- Diabetes medications (≥ 4 weeks before Day 1, Visit T1)
- Obesity medications (≥ 4 weeks before Day 1, Visit T1)

Other concomitant medications and doses must be stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety.

8.5. Treatment Compliance

8.5.1. Screening Compliance

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

8.5.2. Placebo Run-in and Treatment Period Adherence

At the Week -1 (S3) visit in the placebo and ezetimibe run-in period and at each of the subsequent patient visits, designated clinical site staff will assess patients for ezetimibe and IMP adherence by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. Prior to randomization, during the ezetimibe and single-blind run-in period, patients with $\leq 80\%$ adherence to either ezetimibe or single-blind placebo and/or who experienced an AE judged at least possibly related to ezetimibe and/or single-blind placebo will not go on to randomization.

After randomization, if the patient has not taken all doses of study drug 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. Following randomization, 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.

8.6. Blinding

Patients who satisfy all entry criteria during the screening, complete treatment with ezetimibe 10 mg and the single-blind placebo during the run-in period, and meet the lipid, safety,

tolerability, and drug adherence measures will be randomized to receive either bempedoic acid or placebo at Week 0 (Visit T1). The investigator or designee will contact IWRS at this visit to randomize the patient into the study.

After patients have been randomized, study drug, as assigned by the IWRS, will be administered in a double-blind fashion. 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. Unblinded user(s) will be designated for each clinical site and at the Sponsor (or designee) as needed. Unblinded individuals will be provided IWRS access allowing them the ability to perform emergency unblinding of treatment for an individual patient. An affirmative entry of the user's login details will be required before the treatment group is displayed. Unblinding at the clinical site for any other reason will be considered a protocol deviation. Unblinded treatments for patients will NOT automatically discontinue the patient from the study. To discontinue the patient from the study, the appropriate clinical site personnel will need to register the 'discontinuation' visit separately.

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 that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, or CRO.

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: 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 SAE criteria will be reported as SAEs.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety data from this and other ongoing studies of bempedoic acid.

8.7. 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, as per medical judgement.

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks was generally well tolerated. One female patient with homozygous sitosterolemia took an accidental overdose of ezetimibe 120 mg/day for 28 days with no reported clinical or laboratory adverse events. In the event of an overdose, symptomatic and supportive measures should be employed [14].

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Investigational Medicinal Product Supply and Control

The Sponsor will supply the 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 medical identification (MED ID) number (an identifier on the study drug packaging) will be obtained via IWRS and used to select placebo 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 one 100-day supply increments (one 100-day supply bottle) to patients by appropriate clinical site personnel at Week 0 (Visit T1). Patients will bring their bottle at each subsequent visit for tablets to be counted by study personnel. After tablets have been counted, the same bottle will be reissued to patients at Week 4 (Visit T2) and Week 8 (Visit T3) with the bottle being returned to study site at Week 12/EOS for the final count.

A 30-day supply of open-label ezetimibe 10 mg will be dispensed at Week -4 (Visit S2) for the run-in period of the study. A 90-day supply will be dispensed at Week 0 (Visit T1). Patients will bring their bottle to each subsequent visit for tablets to be counted by study personnel. After tablets have been counted, the same bottle will be reissued to patients at Week 4 (Visit T2) and Week 8 (Visit T3) with the bottle being returned to study site at Week 12/EOS for the final count.

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

9.2. Administration of Investigational Medicinal Product

Patients will be instructed to ingest study-supplied ezetimibe 10 mg and single-blind placebo 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. Ezetimibe and IMP may be taken with or without food. On clinic visit days, patients will be instructed to delay ingestion of ezetimibe and IMP until all study procedures have been completed. If a patient arrives at clinic on Visits T2, T3, or T4 without having fasted or having taken ezetimibe and/or IMP before arriving at the clinic, the visit should be rescheduled for the next day or as soon as possible so that the fasting and dosing requirements can be met. Patients will be instructed to return all packaging and unused IMP and ezetimibe at each clinic visit.

If the patient forgets to take ezetimibe and/or IMP at the usual time on nonclinic visit days, it may be taken up to 12 hours later the same day. After that time, the patient should not take the medication that day and should resume ingestion of the medicine the following day. If a patient fails to take ezetimibe and/or IMP, details describing the reasons for nondosing should be documented in the patient's medical records and electronic case report form (eCRF). Extra ezetimibe and IMP (7 extra days per bottle) will be provided and can be used, if needed, prior to

the next visit or to replace a dose of ezetimibe or IMP that cannot be used because it is lost or damaged.

9.3. Investigational Medicinal Product Accountability

Accurate records of the receipt of all IMP and Sponsor-supplied ezetimibe shipped by the Sponsor (or designee) and the disposition of that IMP and ezetimibe must be maintained.

IMP/ezetimibe records or logs must comply with applicable regulations, local law, and guidelines, and should include:

- Amount received/placed in storage area
- Amount currently in storage area
- MED ID number
- Dates and initials of person(s) responsible for inventory (including entry/movement/disposition)
- Date and amount of dispensed to each patient, including unique patient identifiers
- Date was returned by patient, assessment of compliance, and relevant documentation of discrepancies
- Nonstudy disposition (eg, lost, broken, wasted)
- Amount returned to Sponsor/Sponsor's designee/destroyed or amount destroyed per local standard operating procedure (SOP) following accountability by site monitor.

9.4. Investigational Medicinal Product Handling and Disposal

Upon completion or termination of the study, all used and unused IMP with the IMP packaging and ezetimibe must be returned to the Sponsor (or designee) for eventual destruction unless otherwise authorized by the Sponsor. All IMP returns must be accompanied by the appropriate documentation.

10. STUDY PROCEDURES

10.1. 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 IRB or IEC.

10.2. Procedures and Schedule of Assessments

Patients who provide informed consent and sign the ICD will be eligible to begin screening for the study. The study is comprised of 3 distinct periods: screening, single-blind placebo and ezetimibe run-in, and double-blind treatment.

The schedule of study events is provided in [Appendix 1](#). However, a patient can be seen at any time for reasons of safety.

Data will be captured on eCRFs. Randomization, drug supply (re)ordering, and patient tracking will occur via IWRS. Instructions for these systems will be provided separately.

10.2.1. Screening Week -5 (Visit S1; Day -35 to \pm 7 days)

The screening period will begin with a screening visit that will occur approximately 5 weeks prior to randomization. At the investigator's discretion, screening may be extended for an additional 4 weeks, if needed, to adjust background medical therapy or for other reasons as specified in the protocol. Visit S1 will allow the investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent ([Section 10.1](#)), the patient will undergo the following assessments and procedures at Visit S1:

- Informed consent
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Demographics
- Clinically relevant medical history
- Concomitant and prohibited medication review
- Weight (kg)
- Height (cm), BMI (kg/m^2)
- Vital signs
- Serum pregnancy test (on appropriate female patients)/FSH
- TSH
- Clinical safety laboratory evaluations (hematology, blood chemistry, coagulation, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)

- HbA_{1C}
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their background LMT for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. Patients who fail to meet any entry criterion that can be assessed at Visit S1 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).

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

10.2.2. Placebo and Ezetimibe Run in Week -4 (Visit S2; Day -28 to ± 3 days)

Prior to scheduling Visit S2, review the screening clinical results to evaluate whether the patient continues to meet eligibility criteria.

- If the patient meets eligibility criteria, then schedule the Visit S2 and proceed with the Visit S2 procedures

Patients will undergo the following assessments and procedures at Visit S2:

- Review of all inclusion/exclusion criteria that can be assessed at this time
- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints (starting from signing of the informed consent document)
- Physical examination
- Electrocardiogram (ECG)
- Vital signs
- Serology (including HBsAg, hepatitis C antibody)
- Conduct diet and exercise counseling
- Dispense ezetimibe 10 mg and single-blind placebo with instructions. If the patient is already taking ezetimibe, instruct patient to stop taking their personal supply of ezetimibe and to start taking study-supplied ezetimibe.
- Schedule next visit

10.2.3. Placebo and Ezetimibe Run-in Week -1 (Visit S3; Day -7 to ± 3 days)

Patients will undergo the following assessments and procedures at Visit S3:

- Review of all inclusion/exclusion criteria

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- For patients who were not taking ezetimibe at Week -5, Visit S1, measure CK and blood chemistry
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Conduct diet and exercise counseling
- Assessment and recording of drug compliance with both single-blind placebo and study-supplied ezetimibe
- Schedule next visit

10.2.4. Treatment Week 0 (Visit T1; Day 1)

Prior to scheduling Visit T1, review the information collected at Visits S1, S2, and S3 to evaluate whether the patient continues to meet eligibility criteria.

- If the patient meets eligibility criteria, then schedule Visit T1 and proceed with the Visit T1 procedures

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 any entry criterion prior to randomization are considered to be screen failures, will not be randomized into a treatment group, and are not required to return for additional visits. 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.

Patients will undergo the following assessments and procedures at Visit T1:

- Review inclusion/exclusion criteria to establish patient eligibility
- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Weight
- Vital signs
- Urine pregnancy test (for females of childbearing potential)
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Special fasting lipids and other biomarkers (including apoB and hs-CRP)
- HbA_{1C}
- Conduct diet and exercise counseling
- Randomization

- Double-blind drug dispensing with instructions – bempedoic acid 180 mg and matching placebo
- Ezetimibe dispensing
- Drug return and recording of drug compliance
- Dispense a new bottle of double-blind IMP and ezetimibe 10 mg
- Schedule next visit

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

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.3](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to [Section 10.3.1](#) for the list of the required assessments. The patient will be asked to continue to be followed using the protocol-specified visit schedule.

Patients refusing to continue to return to the clinic for protocol assessments after withdrawing from IMP treatment will be asked to participate in phone calls from the site at protocol-specified visits, or at a minimum at 12 weeks, to inquire about the patient's current health status and collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If the patient consents for telephone contacts, schedule the next protocol-specified visit.

Patients will undergo the following assessments and procedures at Visit T2:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Vital signs
- Clinical safety 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
- Conduct diet and exercise counseling
- Record unused IMP and ezetimibe and reissue study drug bottles
- Schedule next visit

10.2.6. Treatment Week 8 (Visit T3; Day 57 ±3 days)

If the patient is withdrawing early from the study at this visit, proceed to [Section 10.3](#) for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to [Section 10.3.1](#) for the list of the required assessments. The patient will be asked to continue to be followed using the protocol-specified visit schedule.

Patients refusing to continue to return to the clinic for safety assessments after withdrawing from IMP treatment will be asked to participate in phone calls from the site at protocol-specified visits, or at a minimum at 12 weeks, to inquire about the patient's current health status and collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If the patient consents for telephone contacts, schedule the next protocol-specified visit.

Patients will undergo the following assessments and procedures at Visit T3:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Vital signs
- Clinical safety 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
- Conduct diet and exercise counseling
- Record unused study drug and reissue IMP and ezetimibe bottles
- Schedule next visit

10.2.7. Treatment Week 12/EOS (Visit T4; Day 85 \pm 3 days)

Patients will undergo the following assessments and procedures at Week 12 (Visit T4) when completing an EOS visit or withdrawing from study (early withdrawal).

Patients will undergo the following assessments and procedures at Visit T4:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs and potential clinical endpoints
- Physical Exam
- Weight (kg)
- 12-lead ECG
- Vital Signs
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Special fasting lipids and other biomarkers (including apoB and hs-CRP)
- HbA_{1C}
- PK sample prior to dose
- Conduct diet and exercise counseling
- Drug return and recording of drug compliance

- Complete study status in IWRS (ie, early withdrawal or completed study).

10.3. Subject Withdrawal Criteria

10.3.1. Early Withdrawal from the Study

Patients must remain in the study until the last scheduled visit at Week 12 (Visit T4) to be considered as having completed participation in the study.

Patients who withdraw from IMP and/or ezetimibe prior to Week 12 (Visit T4) 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 [Appendix 1](#)).

Patients who temporarily withdraw from IMP and/or ezetimibe prior to Week 12 (Visit T4) for any reason may restart IMP and/or ezetimibe providing that (1) the patient and the investigator are in agreement regarding this course of action, (2) the patient has been off of IMP for 4 weeks or less; and (3) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

Patients who refuse 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 [Appendix 1](#)), or at a minimum at 12 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 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.

10.3.2. Procedures for Early Withdrawal

If a patient withdraws or is removed from the study for any reason, the patient should complete an End of Study visit. 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. Except in the case of a medical emergency, the procedures and assessments detailed in [Section 10.3](#) will be performed upon the discontinuation of the study.

11. ASSESSMENT OF SAFETY

11.1. 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.

11.1.1. 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.

11.1.2. Vital Signs

Vital signs will include diastolic and systolic blood pressure 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, blood pressure 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.

11.1.3. Weight, Height, and Body Mass Index

Body weight will be measured in the morning using consistent scales while the patient is fasting, after voiding, and without shoes and outerwear (eg, coats).

Height will be measured using standard clinic procedures.

BMI will be calculated using the formula:

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

11.1.4. Physical Examination

Physical examinations (PE) 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 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.

Note: Additional information will be collected regarding muscle-related AEs. See [Section 12.7.2](#).

11.1.5. Electrocardiogram

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

11.1.5.1. 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. The event will be 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.

11.1.6. Clinical Laboratory Tests

11.1.6.1. 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](#). Collection schedule, schedule of laboratory parameters by visit, and instructions are in the Clinical Laboratory Manual provided by the Central Laboratory.

Table 3: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Hematology</u> <ul style="list-style-type: none"> • 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 %) 	<u>Blood Chemistry (serum, fasting)</u> <ul style="list-style-type: none"> • Albumin (Alb) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]) • Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT]) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO₂) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total bilirubin (TB)^a • Total protein • Uric acid
<u>Urinalysis (Dipstick)</u> <ul style="list-style-type: none"> • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen 	

Table 3: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> Bacteria Casts Crystals Epithelial cells RBC WBC 	<u>Coagulation (screening for all patients, T1 and 3-5 days after T1 in patients receiving anticoagulation therapy, only)</u> <ul style="list-style-type: none"> Prothrombin time (PT) International normalized ratio (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg) Hepatitis C virus (HCV)^b Serum pregnancy test (only for females of childbearing potential) Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) Urine pregnancy test prior to randomization (for female of child bearing potential) Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1c} (HbA_{1c})

^a If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

^b If hepatitis C antibody (HCV-AB) is positive, a reflex HCV RNA will be performed to rule out active disease.

11.1.6.2. Sample Collection, Storage, and Shipping

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

Blood draws for lipids, TG, and glucose must meet the fasting criterion listed below. If this criterion has not been met, these blood samples will NOT be collected. If this criterion can be met by rescheduling the clinic visit to occur within 3 days, the lipid, TG, and/or glucose 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)

11.1.6.3. General Monitoring and Management of Abnormal Clinical Labs

It is the investigators' 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 (as described below), and if yes, an appropriate eCRF will be completed. 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. Specific monitoring and management guidelines for laboratories of special interest are outlined in the sections below.

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

11.1.6.3.1. Monitoring and Management of Elevated Liver Function Tests

If at any time after randomization a patient experiences a new ALT and/or AST $>3 \times$ ULN, the patient will undergo repeat confirmatory liver function test (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), hepatitis C virus (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 $>3 \times$ 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 $>5 \times$ ULN, 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 [Appendix 1](#)) or more frequently as determined by the investigator.
- If repeat LFT assessment confirms ALT and/or AST $>3 \times$ ULN in addition to any of the following, the patient should be given no further IMP treatment, but will be asked

to continue to be followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)) or more frequently as determined by the investigator:

- TB $>2 \times$ ULN

Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of $2 \times$ ULN will be based upon direct (conjugated) bilirubin.

- INR $>1.5 \times$ 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

11.1.6.3.2. 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 m²) 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 [Appendix 1](#))

11.1.6.3.3. Monitoring and Management of Hemoglobin Change

If at any time after randomization a patient experiences a Hgb 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 Sponsor 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 IMP treatment. The patient will return at 1-week intervals after withdrawing from IMP treatment for additional Hgb measurement until the level returns to baseline or reaches a satisfactory conclusion.
- If the patient is withdrawn from IMP treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)).

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

11.1.6.3.4. Monitoring and Management of Elevated Creatine Kinase

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, 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 and study-supplied ezetimibe should be discontinued.
- If symptomatic, the following steps should be completed:
 - Hold IMP and study-supplied ezetimibe
 - 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 IMP once CK returns to baseline levels
 - If no alternative explanation exists, consideration should be given to withdrawing the patient from IMP 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:
 - $>10 \times \text{ULN}$, even in the absence of symptoms.
 - In all cases, evaluate the signs/symptoms and laboratory evaluations as outlined above.
- If the patient is withdrawn from IMP treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)).

11.1.6.3.5. Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

Patients will be educated on the signs and symptoms of hypoglycemia. If such signs and symptoms are experienced, patients will be instructed to report these signs and symptoms to the investigator.

During each study visit, patients will be reminded to report all signs and symptoms associated with hypoglycemia to the investigator. For each occurrence of patient-reported signs and symptoms associated with hypoglycemia, the investigator will discuss these symptoms with the patient and assess whether they are attributable to hypoglycemia or to another potential cause. All investigator-confirmed occurrences of hypoglycemia will be recorded as an AE. All occurrences of signs and symptoms that are not confirmed by the investigator to be attributable to hypoglycemia will be reported using the appropriate diagnosis.

Clinical laboratories will be assessed to determine any signs of anion gap metabolic acidosis. If laboratories are consistent with metabolic acidosis, immediate follow up with the patient for further medical evaluation of the acidosis. This event should be captured as an AE.

11.1.6.3.6. 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 IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule (see [Appendix 1](#)).
- Please see the Clinical Laboratory Manual and [Section 11.1.6.2](#) for sample collection and instructions.

11.1.6.4. Pharmacokinetic Assessments

Pharmacokinetic assessments to measure plasma concentrations of ETC-1002 and its metabolite ESP15228 will be conducted from 6 mL whole blood samples collected. At the time of sample

collection, the date and time of blood draw and the last 2 doses of study medication will be collected. Pharmacokinetic sample analyses for ETC-1002 and ESP15228 will be conducted by the bioanalytical laboratory.

11.1.6.5. Collection and Assessment of Pharmacokinetic Samples

Pharmacokinetic samples will be collected from patients prior to dose at Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4), dosing time and PK sampling time must be documented, for use in further developing the population PK model.

Plasma concentrations of ETC-1002 and its metabolite (ESP15228) will be determined using validated methods. Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, "Plasma PK"). See the study laboratory manual for further instructions.

11.1.6.6. Shipment of Pharmacokinetic Samples

Plasma PK samples will be shipped frozen on dry ice according to instructions provided in the laboratory manual.

11.1.6.7. Total Blood Volume of Clinical Laboratory and Pharmacokinetic 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, PK, efficacy, and biomarker assessment. Total whole blood volume collected over the study duration is not to exceed approximately 250 mL for each patient.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

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 11.2.2](#))

11.2.2. 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).

11.2.3. 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 through 30 days following the last dose of IMP to the investigator. Any SAE that occurs within 30 days following the last study visit should be reported to the Sponsor per [Section 11.3](#). 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.

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 change 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.

11.2.4. Severity

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.

11.2.5. Relationship

It is the investigator's responsibility to assess the relationship of the AE to both the IMP and ezetimibe. The degree of "relatedness" of the AE to the IMP and ezetimibe should 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.

11.2.6. 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 11.3](#)).

11.2.7. Treatment-Emergent Adverse Events

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

11.2.7.1. 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 and/or prolongation of hospitalization 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 also 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.

11.2.7.2. 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 nonserious AE on the appropriate eCRF page

11.2.7.3. 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 local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

11.3. Reporting Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following the last dose of IMP (for most patients 30 days following their Week 12 visit), must be reported by the principal investigator or designee to the authorized 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 provided SAE form and submit it to the safety designee within 24 hours of becoming aware of the occurrence.

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 designee.

11.3.1. 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 11.3](#). 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

11.3.2. 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 detailed in [Section 11.3](#).

11.3.3. Reports of Pregnancy

Although not considered an SAE (unless the event occurs with a serious outcome), pregnancy information on female patients will be collected by the authorized safety designee. If a female patient becomes pregnant during the course of the study, study treatment should be discontinued immediately. The principal investigator or designee must complete and submit the Pregnancy Report Form within 24 hours of awareness of the pregnancy. In addition, patients who become pregnant will complete the Week 12/End of Study evaluations according to [Appendix 1](#). Whenever possible, pregnancies should be followed until outcome and the Pregnancy Outcome Reporting Form submitted to the safety designee once the outcome is known.

11.4. Adverse Events of Special Interest

Adverse events of special interest (AESI) include metabolic acidosis (clinical laboratories), hepatic, muscular (AE and CK evaluation), new onset diabetes/hyperglycemia, renal, cardiovascular, and neurocognitive/neurologic events. Based on previous experience with bempedoic acid, uric acid and hemoglobin will be closely monitored. Safety monitoring guidelines for hemoglobin are detailed in [Section 11.1.6.3.3](#). Specific monitoring guidelines are provided in the case of AEs uncovered through laboratory evaluations. Patients are to be queried at each study visit regarding changes in cognition and or signs/symptoms of hypoglycemia.

The protocol procedures included in the bempedoic acid clinical studies are part of standard clinical care for patients with elevated LDL-C and also address the potential and theoretic risks of bempedoic acid.

All bempedoic acid studies will include standard pharmacovigilance including evaluation of AEs, PE findings, vital signs, and laboratory assessments. Cardiovascular events will be adjudicated by an independent CEC in accordance with a prespecified charter. [REDACTED]

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11.5. Data Monitoring Committee

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.

11.6. Clinical Event Committee

A blinded independent expert CEC will adjudicate designated 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.

11.7. Assessment of Lipid Endpoints

11.7.1. Lipid Parameters

Basic fasting lipid samples will be collected during Screening (Visits S1 and S3) and at the 4 double-blind treatment visits (Visits T1, T2, T3, and T4). Lipid assessments will be performed as follows:

- Calculated TC, LDL-C, HDL-C, non-HDL-C, and TG.
 - 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.

Additional fasting lipids and other biomarkers, including apoB and hs-CRP, will be collected at Visits T1 and T4.

11.7.2. Clinical Safety Laboratory Tests

Clinical Safety laboratory samples will be collected Screening (Visit S1) and at the 4 double-blind treatment visits (Visits T1, T2, T3, and T4).

Blood draws for lipids (and glucose) must meet the criteria below. If these criteria have not been met, these blood samples will NOT be collected. If these criteria can be met by rescheduling clinic visit to occur within 3 days, these 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)

Patients are encouraged to be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in [Table 4](#). 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 11.1.6](#).

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 4: Clinical Laboratory Parameters (Lipids) and Cardiometabolic Biomarkers

Clinical Laboratory Test	Clinical Laboratory Test
<u>Basic Lipid Parameters</u> <ul style="list-style-type: none">• Total cholesterol (TC)• Calculated low-density lipoprotein cholesterol (LDL-C)• High-density lipoprotein cholesterol (HDL-C)• Non-high-density lipoprotein cholesterol (non-HDL-C)• Triglycerides (TG)	<u>Other Parameters</u> <ul style="list-style-type: none">• High-sensitivity C-reactive protein (hs-CRP)• apoB

12. STATISTICS

12.1. 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 two documents in the plans for data analysis, and the protocol will be amended, if needed. The SAP will be included as an appendix in the clinical study report for this protocol.

12.2. Determination of Sample Size

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

The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group is expected to provide more than 95% power to detect a difference of 15% in the percent change from baseline to Week 12 in calculated LDL-C between the bempedoic acid treatment group and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15 %. The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group gives a total study sample size of 225.

12.3. 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 their actual treatment.

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.

12.4. Disposition, Demographics, and Baseline Characteristics

Disposition, including reason for withdrawal from the IMP or 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.

12.5. Primary Efficacy Analysis

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

Baseline LDL-C 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 as a factor 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 correct 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. Imputed datasets will be analyzed using ANCOVA with treatment as a factor 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. 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. A confirmatory analysis using observed data only will also be performed for the primary endpoint.

12.6. 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 12 in non-HDL-C
3. Test the percent change from baseline to Week 12 in TC
4. Test the percent change from baseline to Week 12 in apoB
5. 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 2-sided. Statistical significance at each step is required in order to test the next hypothesis. If the primary efficacy endpoint meets the criteria for statistical significance, then the percent change from baseline to Week 12 in non-HDL-C will be tested; and so forth.

For the remaining secondary efficacy endpoints (percent change from baseline to Week 12 in TG and HDL-C) 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 a similar ANCOVA model for the primary endpoint with treatment group as a factor and the relevant baseline as the covariate.

Baseline for non-HDL-C, HDL-C, TC, and TG 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 the secondary endpoints included in the stepdown testing procedure, while only observed data analysis will be used for other secondary and tertiary endpoints. For each lipid parameter at each 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 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.

12.7. Safety Endpoints

The summarization of AEs will include only TEAEs. 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, HbA_{1C}, fasting 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 postbaseline time point.

12.7.1. 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 ($\geq 3 \times \text{ULN}$ for either ALT or AST, with accompanying TB $> 2 \times \text{ULN}$ [$\geq 2 \times \text{ULN}$ conjugated/direct] bilirubin will be used in patients with 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.

12.7.2. 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.

12.7.3. Diabetes and Hyperglycemia

Cases of worsening and 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.

12.7.4. 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.

12.7.5. 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.

12.7.6. 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.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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 Good Clinical Practice (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 Food and Drug Administration (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.

13.1. 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

14. 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 13.1](#) for more details regarding the audit process.

15. ETHICS

15.1. 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 Code of Federal Regulations (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.

15.2. Ethical Conduct of Study

The Sponsor personnel, when signing the protocol, attest that the clinical study protocol was subject to critical review and has been approved by the Sponsor ([Appendix 2](#)).

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.

15.3. 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. 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.

15.4. 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.

16. DATA HANDLING AND RECORDKEEPING

16.1. 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.

16.2. 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.

16.3. 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 handwritten 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 following the evaluation.

17. ADMINISTRATIVE CONSIDERATIONS

17.1. Investigators

Investigators 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>

17.2. Study Administrative Structure

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

Central Laboratory:

[REDACTED]

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:

[REDACTED]

Medical and Safety Services:

[REDACTED]

17.3. 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.

17.4. 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.

18. 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.

19. LIST OF REFERENCES

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20. APPENDICES

Appendix 1: Schedule of Events (Patient Visit Schedule)

Appendix 2: Sponsor's Signature

Appendix 3: Investigator's Signature

Appendix 4: Summary of Changes in Amendment 1

Appendix 5: Summary of Changes in Amendment 2

APPENDIX 1. SCHEDULE OF EVENTS (PATIENT VISIT SCHEDULE)

Visit	S1 ¹	S2	S3	T1	T2	T3	T4 ²
Week	-5	-4	-1	0	4	8	12/EOS
Procedure	Day -35 ±7 days	Day -28 ± 3	Day -7 ± 3	Day 1	Day 29 ± 3	Day 57 ± 3	Day 85 ± 3
Informed Consent	X						
Enrollment Criteria	X	X	X	X			
Demographics	X						
Medical History	X						
Concomitant/Prohibited Medications	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X
Physical Exam		X					X
Weight ³	X			X ³			X
Height/BMI	X						
12-Lead ECG ⁴		X					X
Vital Signs ⁵	X	X	X	X	X	X	X
Serology ⁶		X					
Serum Pregnancy/FSH ⁷	X						
Urine Pregnancy ⁷				X			
TSH	X						
Clinical Safety Labs ⁸	X		X	X	X	X	X
Basic Fasting Lipids ⁹	X		X	X	X	X	X
Special Fasting Lipids and Other Biomarkers ¹⁰				X			X
HbA _{1C}	X			X			X
PK sample (prior to IMP dosing)					X	X	X
Diet and exercise counseling	X	X	X	X	X	X	X
Randomization				X			
Single Blind/Ezetimibe Drug Dispensing		X		X ¹¹			
Double Blind Drug Dispensing				X			
Drug Return ¹²			X	X	X	X	X

BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone, HbA_{1C} = hepatitis B surface antigen; PK = pharmacokinetics; TSH = thyroid-stimulating hormone.

- ¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet TG criterion. If this optional visit is completed, the repeat TG value will be used to determine eligibility.
- ² All procedures will be completed at end of study or early termination.
- ³ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).
- ⁴ Single 12-lead ECG will be collected prior to any blood sample collection.
- ⁵ Vital signs will include SBP, DBP, and HR, and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.
- ⁶ Serology for Hep B antigen, Hep C antibody.
- ⁷ FSH completed in appropriate postmenopausal women only; pregnancy test completed in non-postmenopausal women only.
- ⁸ Clinical safety labs include hematology, blood chemistry, and urinalysis. Coagulation panel at S1 only, unless receiving anticoagulants (then test at T1 and repeat 3-5 days after starting IMP). For patients not taking ezetimibe at S1, measure blood chemistry and CK only at S3.
- ⁹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides.
- ¹⁰ Includes apoB and hs-CRP.
- ¹¹ Ezetimibe dispensing only.
- ¹² Record unused IMP and ezetimibe and reissue study drug bottles at Visits T1 (ezetimibe only), T2, and T3. Perform final drug count at Visit T4.

APPENDIX 2. SPONSOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins

Study Number: 1002-048

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 Signature]

Date: 28 Mar 2017

[Redacted Signature]

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins

Study Number: 1002-048

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:

A large black rectangular redaction box covering the signature of the person.

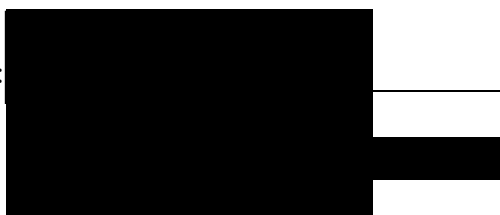
Date: 04 Mar 2017

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins

Study Number: 1002-048

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: _____

A large black rectangular redaction box covering the signature of the person.

3/4/2017

A small black rectangular redaction box covering the date.

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins

Study Number: 1002-048

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 Signature]

Date: _____

3/04/17

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins

Study Number: 1002-048

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. SUMMARY OF CHANGES AMENDMENT 1

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-048

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C

Protocol Version Incorporating Current Summary of Changes: Amendment 1: 18 January 2017

Preceding Protocol Version: Original Protocol: 22 September 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:

- Added a line for Amendment 1 version and date to reflect amendment version details.
- Revised inclusion #5 under Section 7.1, Subject Inclusion Criteria, to revise the definition of abstinence to reflect guidance from the Heads of Medicines Agency.
- Added the revised inclusion criteria #5 to the Synopsis
- Changed names and titles of Sponsor representatives providing signage on the protocol amendment

CHANGE 1 REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page: Version

Original Text:

Version	Date
Original Protocol:	22 September 2016

New Text:

Version	Date
<i>Amendment 1:</i>	<i>18 January 2017</i>

CHANGE 2 REVISION OF INCLUSION CRITERIA

Location:

Synopsis, Diagnosis and criteria for patient eligibility, Inclusion Criteria

New Text:

5. *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 willing to use 1 acceptable method of birth control including:*
 - *oral, implantable, or topical 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).*

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

Location:

Section 7.1, Subject Inclusion Criteria

Original Text:

5. 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 willing to use 1 acceptable method of birth control including:
 - Oral, implantable, or topical 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)

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

New Text:

5. 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 willing to use 1 acceptable method of birth control including:
 - oral, implantable, or topical 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)~~
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).

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

CHANGE 3 REMOVED FINAL DATE

Location:

Appendix 2: Final Date, all pages within Appendix 2

Original text:

Final Date: 22 September 2016

New text:

Final Date: ~~22 September 2016~~

CHANGE 4 CHANGE IN SPONSOR REPRESENTATIVES PROVIDING PROTOCOL SIGNAGE

Location:

Appendix 2: Sponsor Signatures

Original text:

Signed: _____ Date: _____
Sharon Watling, PharmD
Senior Director, Clinical Development
Esperion Therapeutics, Inc.

New text:

Signed: _____ Date: _____
~~Sharon Watling, PharmD~~ **LeAnne Bloedon, MS, RD**
Senior Director, Clinical Development
Esperion Therapeutics, Inc.

Original text:

Signed: _____ Date: _____
Mary McGowan, MD
Chief Medical Officer
Esperion Therapeutics, Inc.

New text:

Signed: _____ Date: _____
~~Mary McGowan,~~ **Ricardo Dent-Acosta, MD**
~~Chief Medical Officer~~ **Vice President, Clinical Development**
Esperion Therapeutics, Inc.

APPENDIX 5. SUMMARY OF CHANGES AMENDMENT 2

SUMMARY OF CHANGES CLINICAL STUDY PROTOCOL

Study Number: 1002-048

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less than Low Dose Statins

Protocol Version Incorporating Current Summary of Changes: Amendment 2: 10 February 2017

Preceding Protocol Version: Amendment 1: 18 January 2017

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:

- Added a line for Amendment 2 version and date to reflect amendment version details.
- Changed protocol title to more accurately reflect the study population.
- Updated bempedoic acid mechanism of action.
- Revised inclusion criteria #3 to allow enrollment of ezetimibe naïve patients with LDL-C ≥ 120 mg/dL at Week -5, Visit S1; included LDL mmol/L as well as mg/dL values.

- Added injectables as an allowable form of hormonal contraception and requirement that women use 2 rather than 1 form of acceptable contraception based on a regulatory request received through the Voluntary Harmonization Procedure in Europe (no new data led to this decision).
- Clarified time period during which subjects should not intend to become pregnant (starting at minimum on Day 1 and continuing for at least 30 days after last dose of study drug).
- Added exclusion criteria to cover previous intolerance to ezetimibe.
- Added exclusion criteria for patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9.
- Excluded use of CETP inhibitors.
- Changed exclusion time period for mipomersen to 6 months.
- Removed the allowance to rescreen if LDL-C criteria at S1 is not met.
- Extended screening an additional 4 weeks if needed to adjust background therapy.
- Removed collection of PK at Day 0; specified collection of PK samples prior to IMP dosing.
- Added requirement to S3 (Week -1) Visit that LDL-C ≥ 70 mg/dL.
- Added chemistry panel and CK to Visit S3 (Week -1) given inclusion of ezetimibe naïve patients.
- Removed optional genetic sampling.
- Removed instructions to reserve samples.
- Corrected windowing of allowable and prohibited medications to be consistent between entry criteria and protocol body.
- Removed lipids other than LDL-C as a specified tertiary endpoint.
- Removed manufacturing contact details (will be in pharmacy manual).
- Added text on the administration of study supplied ezetimibe, including assessment of relationship of AEs to both IMP and ezetimibe.
- Changed monitoring of CK for asymptomatic patients per FDA request.
- Revised safety endpoints.
- Revised statistical sections to clarify level of significance standard deviation, methods for imputation of missing data, and application of ANCOVA model for primary and secondary endpoints.
- Made administrative changes made throughout protocol where required to correct inconsistencies, add clarification, or correct errors.

CHANGE 1 REVISION OF PROTOCOL TITLE AND TITLE PAGE VERSION INFORMATION

Location:

Title page

Original Text:

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C

Version	Date
Amendment 1:	18 January 2017

New Text:

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C *on Low Dose or Less than Low Dose Statins*

Version	Date
Original Protocol	22 September 2016
Amendment 1:	18 January 2017
Amendment 2:	10 February 2017

CHANGE 2 SYNOPSIS REVISIONS

Location:

Section 2, Synopsis

(Only changes specific to Synopsis are noted here. Changes that apply to both Synopsis and CSR body sections are noted under 'Location:')

Original Text:

Secondary:

- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on
 - non-high-density lipoprotein cholesterol (non-HDL-C),
 - total cholesterol (TC),
 - apolipoprotein B (apoB), and
 - high-sensitivity C-reactive protein (hs-CRP)

- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)
- To evaluate 12-week safety and tolerability of bempedoic acid 180 mg/day compared with placebo

Tertiary:

- To evaluate the effects of 4- and 8-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on
 - LDL-C
 - Non-HDL-C
 - TC
 - TG
 - HDL-C

New Text:

Secondary:

- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on
 - non-high-density lipoprotein cholesterol (non-HDL-C),
 - total cholesterol (TC),
 - apolipoprotein B (apoB), and
 - high-sensitivity C-reactive protein (hs-CRP)
- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) *when added to ezetimibe*
- To evaluate 12-week safety and tolerability of bempedoic acid 180 mg/day compared with placebo *when added to ezetimibe*

Tertiary:

- To evaluate the effects of ~~4- and 8-week~~ treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy *at 4 and 8 weeks on the following parameters:*
 - LDL-C
 - Non-HDL-C
 - TC
 - TG
 - HDL-C

Original Text:

Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter study that will be conducted in North America and Europe. Patients on maximally tolerated background lipid-modifying therapy (LMT) that includes ezetimibe and a maximally tolerated statin that is low dose or less than low dose (including patients unable to tolerate a statin at any dose) and who require additional LDL lowering will be eligible for screening. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are not allowed. Screening (Visit S1) will begin 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 as specified in the protocol. Eligible patients will return at Week -4 (Visit S2) to discontinue their current supply of ezetimibe 10 mg and begin treatment with study-supplied ezetimibe 10 mg and single-blind placebo. Patients will continue their other background LMT for the duration of the trial. Patients will return to the clinical site at Week -1 (Visit S3) for assessment of adverse events (AEs) and adherence with study medication (study-supplied ezetimibe and single-blind placebo) and to complete lipid assessments. Approximately 225 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (N = 150) or placebo (N = 75) for 12 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4).

New Text:

Study Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter study that will be conducted in North America and Europe. Patients on ~~maximally tolerated background lipid-modifying therapy (LMT) that includes ezetimibe and a maximally tolerated statin that is low dose or less than low dose~~ **statin therapy** (including patients unable to tolerate a statin at any dose) and who require additional LDL lowering will be eligible for screening. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are not allowed. Screening (Visit S1) will begin 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 as specified in the protocol. Eligible patients will return at Week -4 (Visit S2) to ~~discontinue their current supply of ezetimibe 10 mg and~~ begin treatment with study-supplied ezetimibe 10 mg and single-blind placebo. **Patients already taking ezetimibe 10 mg will switch to study-supplied ezetimibe 10 mg.** Patients will continue their other background **lipid-modifying therapy (LMT)** for the duration of the trial. Patients will return to the clinical site at Week -1 (Visit S3) for assessment of adverse events (AEs) and adherence with study medication (study-supplied ezetimibe and single-blind placebo) and to complete lipid assessments. Approximately 225 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (N = 150) or placebo (N = 75) for 12 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4).

Original Text:

Statistical Methods:

Sample Size

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

The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group is expected to provide more than 95% power to detect a difference of 15% in the percent change from baseline to Week 12 in calculated LDL-C between the bempedoic acid treatment group and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15 mg/dL. The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group gives a total study sample size of 225.

New Text:

Statistical Methods:

Sample Size

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

The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group is expected to provide more than 95% power to detect a difference of 15% in the percent change from baseline to Week 12 in calculated LDL-C between the bempedoic acid

treatment group and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15% ~~mg/dL~~. The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group gives a total study sample size of 225.

Original Text:

Primary Efficacy 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 as a factor 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 used as confirmatory. The PMM will be used to specify different imputation strategies depending on whether or not the patient is still on study treatment. Imputed datasets will be analyzed using ANCOVA with treatment as a factor 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 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 Analysis

For the remaining secondary efficacy endpoints (percent change from baseline to Week 12 in TG and HDL-C) 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.

A significance level of 0.05 will be used; given the large number of tertiary endpoints, the p-values for those endpoints will be considered descriptive.

Change from baseline to Week 12 in LDL-C; and percent change from baseline to Week 12 in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA with treatment group as a factor and the relevant baseline as the covariate. Baseline for non-HDL-C, HDL-C, TC, and TG are defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1), while 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 (no imputation will be performed for missing data). For each lipid parameter at each 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 and absolute change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP; to Weeks 4, 8, and 12, 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.

Safety Analyses

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

The summarization of AEs will include only treatment-emergent AEs (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, 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 postbaseline time point.

New Text:

Primary Efficacy 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 as a factor 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. ***Missing data will be imputed using multiple imputation method that accounts for treatment adherence via*** ~~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 or not the patient is still on study treatment.~~ Imputed datasets will be analyzed using ANCOVA with treatment as a factor and baseline LDL-C as a covariate. Approximately ~~200~~100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. ***For final results, each 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 Analysis

~~For the remaining secondary efficacy endpoints (percent change from baseline to Week 12 in TG and HDL-C) 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.~~

~~A significance level of 0.05 will be used; given the large number of tertiary endpoints, the p-values for those endpoints will be considered descriptive.~~

Absolute and percent cChange from baseline to ***specific time points for*** Week 12 in LDL-C; and percent change from baseline to Week 12 in HDL-C, non-HDL-C, TG, TC, apoB, ***lipid parameters*** and hs-CRP will each be analyzed ***similarly*** using ANCOVA with treatment group as a factor and the relevant baseline as the covariate. Baseline for non-HDL-C, HDL-C, TC, and TG are defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1), while 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 (no imputation will be performed for missing data).~~ For each lipid parameter at each 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 and absolute change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP; to Weeks 4, 8, and 12, 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.

Safety Analyses

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

The summarization of AEs will include only treatment-emergent AEs (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, HbA_{1C}, *fasting* 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 postbaseline time point.

Original Text:

PK and Other biomarkers

PK plasma concentrations will be summarized at predose at Week 0 (Visit T1), Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4).

New Text:

PK and Other biomarkers

PK plasma concentrations *for ETC 1002 and its metabolite ESP15228* will be summarized at ~~predose at Week 0 (Visit T1)~~, Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4).

CHANGE 3 INTRODUCTION REVISIONS

Location:

Section 4.1, Lipid-Regulating Drugs and Cardiovascular Disease

Original Text:

Patients with elevated LDL-C on ezetimibe who are only able to tolerate low dose or less than low dose of statins alone (or demonstrate an inability to tolerate a statin) or in combination with other lipid-modifying therapies and unable to meet their LDL-C treatment goals are the target population for this study.

New Text:

*The target population for this study includes p*Patients with elevated LDL-C ~~on ezetimibe~~ who are only able to tolerate low dose or less than low dose of statins ~~alone (or demonstrate an~~ *(including those not taking a statin due to* inability to tolerate a statin) or in combination with other lipid-modifying therapies ~~and unable to meet their~~ *(in some cases also includes ezetimibe)* *and who require additional LDL-C lowering* treatment goals are the target population for this study.

CHANGE 4 INTRODUCTION REVISIONS

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 enter 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 enter 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 5 ENDPOINT REVISIONS

Location:

Section 5.4.3, Tertiary Efficacy Endpoints and Section 5.4.4, Safety Endpoints

Original Text:

Tertiary endpoints include assessments of percent change and absolute change from baseline in lipid levels at the additional time points of Week 4 (T2) and Week 8 (T3).

1. Percent change from baseline to Weeks 4 and 8 in
 - a. LDL-C
 - b. Non-HDL-C
 - c. TC
 - d. TG
 - e. HDL-C
2. Absolute change from baseline to Weeks 4, 8, and 12 in
 - a. LDL-C
 - b. Non-HDL-C
 - c. TC
 - d. TG
 - e. HDL-C

5.4.4 Safety Endpoints

No statistical analyses will be performed on any of the safety data in this study. The descriptive summaries of AE data, endpoints used to evaluate hepatic, musculoskeletal, diabetes/hyperglycemic, renal, neurocognitive safety, and defined clinical endpoints are described in Section 12.7.

New Text:

Tertiary endpoints include assessments of percent change and absolute change from baseline in lipid levels at the additional time points of Week 4 (T2) and Week 8 (T3).

1. Percent change from baseline to Weeks 4 and 8 in
 - a. LDL-C
 - b. Non-HDL-C
 - c. TC
 - d. TG
 - e. HDL-C
2. Absolute change from baseline to Weeks 4, 8, and 12 in **LDL-C**
 - a. ~~LDL-C~~
 - b. ~~Non-HDL-C~~
 - c. ~~TC~~
 - d. ~~TG~~
 - e. ~~HDL-C~~

5.4.4 Safety Endpoints

- a. *Subject incidence to TEAE*
- b. *Safety laboratory values and vital signs*
- c. *ECG findings*
- d. *Cardiovascular event rates*

~~No statistical analyses will be performed on any of the safety data in this study. The descriptive summaries of AE data, endpoints used to evaluate hepatic, musculoskeletal, diabetes/hyperglycemic, renal, neurocognitive safety, and defined clinical endpoints are described in Section 12.7.~~

CHANGE 6 STUDY DESIGN REVISIONS

Location:

Section 6.1, Overall Study Design

Original Text:

Screening Week -5 (Visit S1) will begin 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 as specified in the protocol. Eligible patients will return to the clinical site at Week -4 (Visit S2) to begin treatment with ezetimibe 10 mg and single-blind placebo.

New Text:

Screening Week -5 (Visit S1) will begin 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 as specified in the protocol. Eligible patients will return to the clinical site at Week -4 (Visit S2) to begin treatment with *study supplied* ezetimibe 10 mg and single-blind placebo. *Patients having their own supply of ezetimibe will switch to study-supplied ezetimibe at this visit.*

CHANGE 7 INCLUSION CRITERIA REVISIONS

Location:

Synopsis; Section 7.1, Subject Inclusion Criteria #3

Original Text:

3. Fasting LDL-C (minimum of 10 hours) at Week -5 (Visit S1) ≥ 100 mg/dL (2.6 mmol/L) on stable background LMT (greater than or equal to 4 weeks prior to screening) requiring further LDL-C lowering.

Note: LDL-C may be repeated 1 time with the screening period extended up to 4 weeks. 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.

New Text:

3. Fasting ~~LDL-C~~ (minimum of 10 hours) *calculated LDL-C* at Week -5 (Visit S1) *as defined by ezetimibe use at screening:*
 - *For patients who have been taking ezetimibe 10 mg daily prior to Week -5 (Visit S1): Fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) on stable background lipid-modifying therapy (LMT; greater than or equal to 4 weeks prior to screening) requiring further LDL-C lowering.*
 - *For patients who have not been taking ezetimibe Week -5 (Visit S1): Fasting LDL-C ≥ 120 mg/dL (3.1 mmol/L) on stable background LMT (greater than or equal to 4 weeks prior to screening).*
 - *All patients must have fasting LDL-C ≥ 70 mg/dL (1.8 mmol/L) at Week -1 (Visit S3)*

~~Note: LDL-C may be repeated 1 time with the screening period extended up to 4 weeks. 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.~~

CHANGE 8 INCLUSION CRITERIA REVISIONS

Location:

Synopsis; Section 7.1, Subject Inclusion Criteria #4 and #5

Original Text:

4. Currently receiving stable (greater than or equal to 4 weeks prior to screening) background maximally tolerated LMT that includes ezetimibe 10 mg daily and maximally tolerated statin dose that does not exceed low dose statin therapy. Patients must report attempting greater than low dose statin therapy and being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered.

New Text:

4. Currently receiving stable (greater than or equal to 4 weeks prior to screening) background ~~maximally tolerated LMT that includes ezetimibe 10 mg daily and maximally tolerated~~ statin dose that does not exceed low dose statin therapy. Patients must report attempting ~~greater than low dose~~ statin therapy and being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered.

Original Text:

- Women of childbearing potential willing to use 1 acceptable method of birth control including:
 - oral, implantable, or topical 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).

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

New Text:

- Women of childbearing potential 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—~~including~~:

- oral, implantable, ***injectable***, or topical 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).

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

CHANGE 9 EXCLUSION CRITERIA REVISIONS

Location:

Synopsis; Section 7.2, Subject Exclusion Criteria #2

Original Text:

2. Recent history of documented clinically significant cardiovascular disease including, but not limited to
 - Within 3 months of screening, myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease
 - Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥ 160 mm Hg and diastolic blood pressure (DBP) ≥ 100 mm Hg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the investigator, the screening period may be extended up to 4 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria
 - Within 3 months of screening, arrhythmia requiring medical intervention
 - Planned revascularization procedures
 - New York Heart Association (NYHA) Class IV heart failure

New Text:

2. Recent history of documented clinically significant cardiovascular disease including, but not limited to
 - Within 3 months of screening (*Week -5 [Visit S1]) or between screening and randomization*, myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease
 - Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥ 160 mm Hg and diastolic blood pressure (DBP) ≥ 100 mm Hg after sitting quietly for 5 minutes. Note: If the initial blood pressure (BP) values meet or exceed the specified level, an additional BP assessment may be completed. If the systolic or the diastolic values continue to meet or exceed the threshold, the patient may not continue screening. However, at the discretion of the investigator, the screening period may be extended up to 4 weeks to allow for a repeat qualifying BP assessment following adjustment of BP medication(s), provided that the patient has been on a stable dose of the BP medication for a minimum of 2 weeks prior to randomization and the repeat BP measurements do not meet the exclusion criteria
 - Within 3 months of screening (*Week -5 [Visit S1]) or between screening and randomization visits*, arrhythmia requiring medical intervention
 - Planned revascularization procedures
 - New York Heart Association (NYHA) Class IV heart failure

CHANGE10 EXCLUSION CRITERIA REVISIONS

Location:

Synopsis; Section 7.2, Subject Exclusion Criteria #15, #17, #21, and #22

Original Text:

15. Use of any experimental or investigational drugs within 30 days prior to screening;
16. Previous enrollment in a bempedoic acid clinical study.
17. Use of any of the following drugs prior to screening or a plan to use these drugs during the study as follows:
 - Within 2 weeks prior to screening
 - Cholestin or red yeast rice-containing products (also known as monascus purpureus extract)
 - Within 4 weeks prior to screening
 - Statin doses exceeding those defined as low dose. Doses exceeding low dose statin therapy are defined as an average daily dose of rosuvastatin greater than 5 mg, atorvastatin greater than 10 mg, simvastatin greater than 10 mg, lovastatin

greater than 20 mg, pravastatin greater than 40 mg, fluvastatin greater than 40 mg, or pitavastatin greater than 2 mg.

- Within 3 months prior to screening:
 - Requirement for mipomersen or lomitapide or apheresis therapy
 - Probenecid or cyclosporine
- Within 4 months prior to screening
 - Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

18. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:

- Hormone replacement (within 6 weeks prior to randomization)
- Thyroid replacement (within 6 weeks prior to randomization)
- Diabetes medications (within 4 weeks prior to randomization)
- Obesity medication (within 3 months prior to randomization)

19. 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.

20. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or Sponsor.

21. Pregnant, breastfeeding, or intending to become pregnant

New Text:

15. Use of any experimental or investigational drugs within 30 days prior to screening.

Patients who have enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9 are excluded;

16. Previous enrollment in a bempedoic acid clinical study.

17. Use of any of the following drugs prior to screening (***Week -5, Visit S1***) or a plan to use these drugs during the study as follows:

- Within 2 weeks prior to screening
 - Cholestin or red yeast rice-containing products (also known as monascus purpureus extract)
- Within 4 weeks prior to screening
 - Statin doses exceeding those defined as low dose. Doses exceeding low dose statin therapy are defined as an average daily dose of rosuvastatin greater than 5 mg, atorvastatin greater than 10 mg, simvastatin greater than 10 mg, lovastatin greater than 20 mg, pravastatin greater than 40 mg, fluvastatin greater than 40 mg, or pitavastatin greater than 2 mg.

- ***Within 6 weeks prior to screening for patients taking a statin***
 - ***Gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label***
 - Within 3 months prior to screening:
 - ~~Requirement for mipomersen or Lomitapide~~ or apheresis therapy
 - Probenecid or cyclosporine
 - Within 4 months prior to screening
 - Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
 - ***Within 6 months prior to screening***
 - ***Mipomersen***
 - ***Cholesteryl ester transfer protein inhibitor (CETP-I) within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months to screening (Week -5, Visit S1)***
18. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
- Hormone replacement (within 6 weeks prior to randomization)
 - Thyroid replacement (within 6 weeks prior to randomization)
 - Diabetes medications (within 4 weeks prior to randomization)
 - Obesity medication (within ***4 weeks***~~3 months~~ prior to randomization)
19. 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.
20. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or Sponsor.
21. Pregnant, breastfeeding, or intending to become pregnant ***within 30 days after study completion or last dose of study drug.***
- 22. Previous intolerance to ezetimibe.***

CHANGE 11 REMOVED REDUNDANT TEXT

Location:

Section 7.3, Patient Lifestyle and Dietary Guidelines

Original Text:

Each dose of investigational medicinal product (IMP) is comprised of 1 tablet from 1 bottle that will be dispensed at each scheduled clinic visit. Study drug should be taken once a day (once

every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples.

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.

New Text:

~~Each dose of investigational medicinal product (IMP) is comprised of 1 tablet from 1 bottle that will be dispensed at each scheduled clinic visit. Study drug should be taken once a day (once every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples.~~

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.

CHANGE 12 CONCOMITANT MEDICATIONS REVISIONS

Location:

Section 8.4.1, Lipid-Regulating Medications and Supplements

Original Text:

Eligible patients will be those currently receiving stable (greater than or equal to 4 weeks prior to screening) background maximally tolerated LMT that includes ezetimibe 10 mg daily and maximally tolerated statin therapy that does not exceed low dose. 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. Very 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.

Patients on ezetimibe and low or very low dose statin or unable to tolerate any statin at any dose are eligible. Patients may continue taking low or very low dose statin therapy throughout the study provided that it is stable (greater than or equal to 4 weeks) and well tolerated. Patients unable to take any dose of statins are also eligible provided that statin therapy has been attempted.

PCSK9 inhibitors are not allowed during the study period.

The ezetimibe and IMP will be study-supplied.

New Text:

Eligible patients will be those currently receiving stable (greater than or equal to 4 weeks prior to screening, **Week -5, Visit S1**) background ~~maximally tolerated LMT that includes ezetimibe 10 mg daily and maximally tolerated~~ statin therapy that does not exceed low dose. 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. Very 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.

~~Patients on ezetimibe and low or very low dose statin or unable to tolerate any statin at any dose are eligible. Patients may continue taking low or very low dose statin therapy throughout the study provided that it is stable (greater than or equal to 4 weeks) and well tolerated. Patients unable to take any dose of statins are also eligible provided that statin therapy has been attempted, as described above.~~

Patients should continue taking their LMT throughout the study.

PCSK9 inhibitors are not allowed during the study period.

The ezetimibe and IMP will be study-supplied. ***Patients on ezetimibe at Visit S1 will stop taking their supply of medication at Visit S2 and begin taking study-supplied ezetimibe.***

CHANGE 13 CONCOMITANT MEDICATIONS REVISIONS

Location:

Section 8.4.2 Prohibited Medications

Original Text:

Patients will not have used the medications (monotherapies or combination therapies) as listed below or use these drugs during the study.

- Cholestin or red yeast rice-containing products (also known as monascus purpureus extract) within 2 weeks prior to screening
- PCSK9-inhibitors within 4 months prior to screening
- Lomitapide, mipomersen, apheresis therapy within 3 months prior to screening

New Text

Patients ***should not use***~~will not have used~~ the ***following*** medications (monotherapies or combination therapies) as listed ***prior to screening as defined in the exclusion criteria and below, or use these drugs at any time*** during the study.

- ***Within 2 weeks prior to screening, Week 5, Visit S1:***
 - Cholestin or red yeast rice-containing products (also known as monascus purpureus extract)~~within 2 weeks prior to screening~~
- ***Within 4 weeks prior to screening, Week -5, Visit S1:***
 - ***Statin dose exceeding low dose as defined under inclusion criteria.***
 - ***New or planned dose changes of systemic corticosteroids***
- ***Within 6 weeks prior to screening, Week -5, Visit S1 for patients taking a statin:***
 - ***Gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label***

- ***Within 3 months prior to screening, Week -5, Visit S1:***
 - ***Lomitapide or apheresis therapy***
 - ***Probenecid or cyclosporine***
- PCSK9-inhibitors within 4 months prior to screening, ***Week -5, Visit S1***
- ~~Lomitapide, mipomersen, apheresis therapy within 3 months prior to screening~~
- ***Mipomersen within 6 months prior to screening, Week -5, Visit S1***
- ***CETP-inhibitors within the last 2 years before screening, Week -5, Visit S1 except for evaceptapib within the last 3 months prior 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 before screening (Week -5, Visit S1). Patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9 are excluded.***

CHANGE 14 CONCOMITANT MEDICATIONS REVISIONS

Location:

Section 8.4.3, Allowable Medications

Original Text:

Other concomitant medications and doses must be stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety.

The following must be stable for a minimum of 6 weeks prior to randomization:

- Postmenopausal hormone therapy
- Thyroid hormone supplements
- Fibrates

The following must be stable for a minimum of 4 weeks prior to screening:

- Hypertriglyceridemia therapy (such as niacin, omega-3 fatty acids)
- LMT (with the exception of PCSK9-inhibitors and greater than low dose statins which are exclusionary)
- Diabetes medications
- 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.

The following must be stable for a minimum of 3 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:

- Antiobesity medications

New Text:

LMT not prohibited are allowed and should remain stable for at least 4 weeks prior to screening (Week -5, Visit S1); fibrates (with the exception of gemfibrozil which is exclusionary in patients taking a statin) should remain stable for at least 6 weeks prior to screening (Week -5, Visit S1). Use of any of the following medications are allowed if started before the randomization visit (Day 1, Visit T1) as defined below and are expected to remain stable through completion of the study:

- ***Hormone replacement therapy (≥6 weeks before Day 1, Visit T1)***
- ***Thyroid replacement therapy (≥6 weeks before Day 1, Visit T1)***
- ***Diabetes medications (≥4 weeks before Day 1, Visit T1)***
- ***Obesity medications (≥4 weeks before Day 1, Visit T1)***

Other concomitant medications and doses must be stable for 2 weeks prior to screening and, if possible, not be adjusted during the study except for reasons of safety.

~~The following must be stable for a minimum of 6 weeks prior to randomization:~~

- ~~• Postmenopausal hormone therapy~~
- ~~• Thyroid hormone supplements~~
- ~~• Fibrates~~

~~The following must be stable for a minimum of 4 weeks prior to screening:~~

- ~~• Hypertriglyceridemia therapy (such as niacin, omega-3 fatty acids)~~
- ~~• LMT (with the exception of PCSK9 inhibitors and greater than low dose statins which are exclusionary)~~
- ~~• Diabetes medications~~
- ~~• 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.~~

~~The following must be stable for a minimum of 3 months prior to screening and, if possible not be adjusted during the study except for reasons of safety:~~

- ~~• Antiobesity medications~~

CHANGE 15 TREATMENT COMPLIANCE REVISIONS

Location:

Section 8.5.2, Placebo Run-in and Treatment Period Adherence

Original Text:

At the Week -1 (S3) visit in the placebo and ezetimibe run-in period and at each of the subsequent patient visits, designated clinical site staff will assess patients for ezetimibe and IMP adherence 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 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. Following randomization, 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. Prior to randomization, during the ezetimibe and single blind run-in period, patients with $\leq 80\%$ adherence and/or who experienced a study drug-related AE will not go on to randomization.

New Text:

At the Week -1 (S3) visit in the placebo and ezetimibe run-in period and at each of the subsequent patient visits, designated clinical site staff will assess patients for ezetimibe and IMP adherence by counting the number of tablets that are returned as unused and by querying the patient with regards to daily intake. ~~¶~~***Prior to randomization, during the ezetimibe and single-blind run-in period, patients with $\leq 80\%$ adherence to either ezetimibe or single-blind placebo and/or who experienced an AE judged at least possibly related to ezetimibe and/or single-blind placebo will not go on to randomization.***

After randomization, if the patient has not taken all doses of study drug 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. Following randomization, 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. ~~Prior to randomization, during the ezetimibe and single-blind run-in period, patients with $\leq 80\%$ adherence and/or who experienced a study drug-related AE will not go on to randomization.~~

CHANGE 16 TREATMENT COMPLIANCE REVISIONS

Location:

Section 9.1, Investigational Medicinal Product Supply and Control

Original Text:

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 one 100-day supply increments (one 100-day supply bottle) to patients by appropriate clinical site

personnel at Week 0 (Visit T1), Week 4 (Visit T2), and Week 8 (Visit T3) and Week 12/EOS (Visit T4).

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

New Text:

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 one 100-day supply increments (one 100-day supply bottle) to patients by appropriate clinical site personnel at Week 0 (Visit T1). *Patients will bring their bottle at each subsequent visit for tablets to be counted by study personnel. After tablets have been counted, the same bottle will be reissued to patients at Week 4 (Visit T2), and Week 8 (Visit T3) and with the bottle being returned to study site at Week 12/EOS for the final count (Visit T4).*

A 30-day supply of open-label ezetimibe 10 mg will be dispensed at Week -4 (Visit S2) for the run-in period of the study. A 90-day supply will be dispensed at Week 0 (Visit T1). Patients will bring their bottle to each subsequent visit for tablets to be counted by study personnel. After tablets have been counted, the same bottle will be reissued to patients at Week 4 (Visit T2) and Week 8 (Visit T3) with the bottle being returned to study site at Week 12/EOS for the final count.

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

CHANGE 17 STUDY PROCEDURES REVISIONS

Location:

Synopsis; Section 10.1, Informed Consent and all other protocol locations as applicable

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 IRB or 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 IRB or 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 18 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.1, Screening Week -5 (Visit S1; Days -42 to -35)

10.2.1 Screening Week -5 (Visit S1; Days -42 to -35)

The screening period will begin with a screening visit that will occur approximately 5 weeks prior to randomization. At the investigator's discretion, screening may be extended for an additional 4 weeks, if needed, to adjust background medical therapy or for other reasons as specified in the protocol. Visit S1 will allow the investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

New Text:

10.2.1 Screening Week -5 (Visit S1; Days ~~-42 to -35~~ to ± 7 days)

The screening period will begin with a screening visit that will occur approximately 5 weeks prior to randomization. At the investigator's discretion, screening may be extended for an additional 4 weeks, if needed, to adjust background medical therapy or for other reasons as specified in the protocol. Visit S1 will allow the investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

Original Text:

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their background statin for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. They should be instructed to stop taking their personal supply of ezetimibe and to take study-supplied ezetimibe. Patients who fail to meet any entry criterion that can be assessed at Visit S1 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).

An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean LDL value will be used to determine eligibility.

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.

New Text:

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their background ~~statin~~ **LMT** for lipid regulation and to maintain consistent diet and exercise patterns throughout the study. ~~They should be instructed to stop taking their personal supply of ezetimibe and to take study-supplied ezetimibe.~~ Patients who fail to meet any entry criterion that can be assessed at Visit S1 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).

~~An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean LDL value will be used to determine eligibility.~~

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

CHANGE 19 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.2, Placebo and Ezetimibe Run in Week -4 (Visit S2; Day -28 to ± 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Visit S2:

- Review of all inclusion/exclusion criteria that can be assessed at this time
- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination
- Electrocardiogram (ECG)
- Vital signs
- Serology (including HBsAg, hepatitis C antibody)
- Conduct diet and exercise counseling
- Single-blind drug dispensing with instructions – ezetimibe 10 mg and placebo
- Schedule next visit

New Text:

Patients will undergo the following assessments and procedures at Visit S2:

- Review of all inclusion/exclusion criteria that can be assessed at this time
- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints*** (starting from signing of the informed consent document)
- Physical examination
- Electrocardiogram (ECG)
- Vital signs
- Serology (including HBsAg, hepatitis C antibody)

- Conduct diet and exercise counseling
- ~~Single-blind drug dispensing with instructions – ezetimibe 10 mg and placebo~~
- ***Dispense ezetimibe 10 mg and single-blind placebo with instructions. If the patient is already taking ezetimibe, instruct patient to stop taking their personal supply of ezetimibe and to start taking study-supplied ezetimibe***
- Schedule next visit

CHANGE 21 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.3 Placebo and Ezetimibe Run-in Week -1 (Visit S3; Day -7 to ± 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Visit S3:

- Review of all inclusion/exclusion criteria
- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Conduct diet and exercise counseling
- Assessment and recording of drug compliance
- Schedule next visit

New Text:

Patients will undergo the following assessments and procedures at Visit S3:

- Review of all inclusion/exclusion criteria
- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints***(~~starting from signing of the informed consent document~~)
- ***For patients who were not taking ezetimibe at Week -5, Visit S1, measure CK and blood chemistry***
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Conduct diet and exercise counseling
- Assessment and recording of drug compliance ***with both single-blind placebo and study-supplied ezetimibe***

- Schedule next visit

CHANGE 21 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.4, Treatment Week 0 (Visit T1; Day 1)

Original Text:

Prior to scheduling Visit T1, review the screening and placebo run-in clinical results to evaluate whether the patient continues to meet eligibility criteria.

- If the patient meets eligibility criteria, then schedule Visit T1 and proceed with the Visit T1 procedures

New Text:

Prior to scheduling Visit T1, review the ~~screening~~ **information collected at Visits S1, S2, and S3** and placebo run-in clinical results to evaluate whether the patient continues to meet eligibility criteria.

- If the patient meets eligibility criteria, then schedule Visit T1 and proceed with the Visit T1 procedures

Original Text:

Patients will undergo the following assessments and procedures at Visit T1:

- Review inclusion/exclusion criteria to establish patient eligibility
- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Weight
- Vital signs
- Urine pregnancy test (for females of childbearing potential)
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Special fasting lipids and other biomarkers (including apoB and hs-CRP)
- HbA_{1C}
- Conduct diet and exercise counseling
- Randomization
- Double-blind drug dispensing with instructions – bempedoic acid 180 mg and matching placebo
- Ezetimibe dispensing

- Drug return and recording of drug compliance
- Schedule next visit

New Text:

Patients will undergo the following assessments and procedures at Visit T1:

- Review inclusion/exclusion criteria to establish patient eligibility
- Concomitant and prohibited medication review (ongoing)
- Assess AEs, *SAEs, and potential clinical endpoints* (~~starting from signing of the informed consent document~~)
- Weight
- Vital signs
- Urine pregnancy test (for females of childbearing potential)
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Special fasting lipids and other biomarkers (including apoB and hs-CRP)
- HbA_{1C}
- Conduct diet and exercise counseling
- Randomization
- Double-blind drug dispensing with instructions – bempedoic acid 180 mg and matching placebo
- Ezetimibe dispensing
- Drug return and recording of drug compliance
- *Dispense a new bottle of double-blind IMP and ezetimibe 10 mg*
- Schedule next visit

CHANGE 22 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.5, Treatment Week 4 (Visit T2; Day 29 ±3 days)

Original Text:

Patients will undergo the following assessments and procedures at Visit T2:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Vital signs

- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Conduct diet and exercise counseling
- Drug return and recording of drug compliance
- Schedule next visit

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments, including basic fasting lipids, after withdrawing from IMP treatment, all assessments except for those procedures pertaining to IMP management (IMP dispensing, IMP compliance, IMP accountability) should be completed.

Note: If this visit is being conducted by telephone contact for patients who have consented to be followed by phone for safety assessments after withdrawing from IMP treatment, collect information as reported by the patient regarding AEs, concomitant medication, and current health status.

New Text:

Patients will undergo the following assessments and procedures at Visit T2:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, *SAEs, and potential clinical endpoints*(starting from signing of the informed consent document)
- Vital signs
- Clinical safety 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 use*
- Conduct diet and exercise counseling
- *Record unused IMP and ezetimibe and reissue study drug bottles* Drug return and recording of drug compliance
- Schedule next visit

~~Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments, including basic fasting lipids, after withdrawing from IMP treatment, all assessments except for those procedures pertaining to IMP management (IMP dispensing, IMP compliance, IMP accountability) should be completed.~~

~~Note: If this visit is being conducted by telephone contact for patients who have consented to be followed by phone for safety assessments after withdrawing from IMP treatment, collect information as reported by the patient regarding AEs, concomitant medication, and current health status.~~

CHANGE 23 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.6, Treatment Week 8 (Visit T3; Day 57 \pm 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Visit T3:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Vital signs
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Conduct diet and exercise counseling
- Drug return and recording of drug compliance
- Schedule next visit

Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments, including basic fasting lipids, after withdrawing from IMP treatment, all assessments except for those procedures pertaining to IMP management (IMP dispensing, IMP compliance, IMP accountability) should be completed.

Note: If this visit is being conducted by telephone contact for patients who have consented to be followed by phone for safety assessments after withdrawing from IMP treatment, collect information as reported by the patient regarding AEs, concomitant medication, and current health status.

New Text:

Patients will undergo the following assessments and procedures at Visit T3:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints***~~(starting from signing of the informed consent document)~~
- Vital signs
- Clinical safety 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***
- Conduct diet and exercise counseling
- ~~Drug return and recording of drug compliance~~ ***Record unused study drug and reissue IMP and ezetimibe bottles***
- Schedule next visit

~~Note: If this visit is being conducted at the site for patients who have consented to be followed for safety assessments, including basic fasting lipids, after withdrawing from IMP treatment, all assessments except for those procedures pertaining to IMP management (IMP dispensing, IMP compliance, IMP accountability) should be completed.~~

~~Note: If this visit is being conducted by telephone contact for patients who have consented to be followed by phone for safety assessments after withdrawing from IMP treatment, collect information as reported by the patient regarding AEs, concomitant medication, and current health status.~~

CHANGE 24 STUDY PROCEDURES REVISIONS

Location:

Section 10.2.7, Treatment Week 12/EOS (Visit T4; Day 85 \pm 3 days)

Original Text:

Patients will undergo the following assessments and procedures at Visit T4:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical Exam
- Weight (kg)
- 12-lead ECG
- Vital Signs
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Special fasting lipids and other biomarkers (including apoB and hs-CRP)
- HbA_{1C}
- Conduct diet and exercise counseling
- Drug return and recording of drug compliance
- Complete study status in IWRS (ie, early withdrawal or completed study).

New Text:

Patients will undergo the following assessments and procedures at Visit T4:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints***(starting from signing of the informed consent document)
- Physical Exam
- Weight (kg)

- 12-lead ECG
- Vital Signs
- Clinical safety laboratory evaluations (hematology, blood chemistry, and urinalysis)
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
- Special fasting lipids and other biomarkers (including apoB and hs-CRP)
- HbA_{1C}
- *PK sample prior to dose*
- Conduct diet and exercise counseling
- Drug return and recording of drug compliance
- Complete study status in IWRS (ie, early withdrawal or completed study).

CHANGE 25 SUBJECT WITHDRAWAL CRITERIA REVISIONS

Location:

Section 10.3.1, Early Withdrawal from the Study

Original Text:

Patients must remain in the study until the last scheduled visit at Week 12 (Visit T4) to be considered as having completed participation in the study.

Patients who withdraw from IMP prior to Week 12 (Visit T4) 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 Appendix 1). The patient must provide consent to be followed in the study after withdrawing from IMP treatment. Protocol procedures to be completed for patients who consent will include those specified at each visit as noted in Schedule of Events (see Appendix 1).

Patients who temporarily withdraw from IMP prior to Week 12 (Visit T4) for any reason may restart IMP providing that (1) the patient and the investigator are in agreement regarding this course of action, (2) the patient has been off of IMP for 4 weeks or less; and (3) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

Patients who do not provide consent 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 Appendix 1), or at a minimum at 12 weeks, to collect information on AEs, concomitant medications, and current health status. The patient must provide consent to be contacted by phone by site personnel for the purposes of assessing current AEs and current health status.

New Text:

Patients must remain in the study until the last scheduled visit at Week 12 (Visit T4) to be considered as having completed participation in the study.

Patients who withdraw from IMP *and/or ezetimibe* prior to Week 12 (Visit T4) 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 Appendix 1). ~~The patient must provide consent to be followed in the study after withdrawing from IMP treatment. Protocol procedures to be completed for patients who consent will include those specified at each visit as noted in Schedule of Events (see Appendix 1).~~

Patients who temporarily withdraw from IMP *and/or ezetimibe* prior to Week 12 (Visit T4) for any reason may restart IMP *and/or ezetimibe* providing that (1) the patient and the investigator are in agreement regarding this course of action, (2) the patient has been off of IMP for 4 weeks or less; and (3) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

Patients who do not provide consent 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 Appendix 1), or at a minimum at 12 weeks, to collect information on AEs, concomitant medications, and current health status. ~~The patient must provide consent to be contacted by phone by site personnel for the purposes of assessing current AEs and current health status.~~

CHANGE 26 ASSESSMENT OF SAFETY REVISIONS

Location:

Synopsis; Section 11.1.6.2: Laboratory Parameters (Safety)

Original Text:

Table 3: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none">• Bacteria• Casts• Crystals• Epithelial cells• RBC• WBC	<u>Coagulation (screening for all patients, T1 and 3-5 days after T1 in patients receiving anticoagulation therapy, only)</u> <ul style="list-style-type: none">• Prothrombin time (PT)• International normalized ratio (INR)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Other Screening Labs</u> <ul style="list-style-type: none"> Hepatitis B surface antigen (HBsAg) Hepatitis C virus (HCV)^b Serum pregnancy test (only for females of childbearing potential) Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) Urine pregnancy test prior to randomization- (for female of child bearing potential) Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> Hemoglobin A_{1C} (HbA_{1C}) Reserve blood samples for potential future measurement of biomarkers Pharmacogenomic (PG) sample (Reserve genetic blood sample; optional)

^a If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

^b If hepatitis C antibody (HCV-AB) is positive, a reflex HCV RNA will be performed to rule out active disease.

11.1.6.2 Other Assessments

All patients will be invited to provide a blood sample for potential future genetic testing, but participation in this portion of the study is optional and only where approved by the IRB/IEC and by local law.

11.1.6.3 Sample Collection, Storage, and Shipping

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

Blood draws for lipids, TG, and glucose must meet the fasting criterion listed below. If this criterion has not been met, these blood samples will NOT be collected. If this criterion can be met by rescheduling the clinic visit to occur within 3 days, the lipid, TG, and/or glucose 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)

New Text:

Table 3: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> <ul style="list-style-type: none"> • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC 	<u>Coagulation (screening for all patients, T1 and 3-5 days after T1 in patients receiving anticoagulation therapy, only)</u> <ul style="list-style-type: none"> • Prothrombin time (PT) • International normalized ratio (INR)
<u>Other Screening Labs</u> <ul style="list-style-type: none"> • Hepatitis B surface antigen (HBsAg) • Hepatitis C virus (HCV)^b • Serum pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) • Urine pregnancy test prior to randomization- (for female of child bearing potential) • Thyroid-stimulating hormone (TSH) 	<u>Additional samples</u> <ul style="list-style-type: none"> • Hemoglobin A_{1C} (HbA_{1C}) • Reserve blood samples for potential future measurement of biomarkers • Pharmacogenomic (PG) sample (Reserve genetic blood sample; optional)

^a If TB $\geq 1.2 \times$ ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

^b If hepatitis C antibody (HCV-AB) is positive, a reflex HCV RNA will be performed to rule out active disease.

~~11.1.6.2 Other Assessments~~

~~All patients will be invited to provide a blood sample for potential future genetic testing, but participation in this portion of the study is optional and only where approved by the IRB/IEC and by local law.~~

~~11.1.6.2~~ 11.1.6.3 Sample Collection, Storage, and Shipping

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

Blood draws for lipids, TG, and glucose must meet the fasting criterion listed below. If this criterion has not been met, these blood samples will NOT be collected. If this criterion can be met by rescheduling the clinic visit to occur within 3 days, the lipid, TG, and/or glucose 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)

CHANGE 27 ASSESSMENT OF SAFETY REVISIONS

Location:

Section 11.1.6.3.1, Monitoring and Management of Elevated Liver Function Test

Original Text:

- If repeat LFT assessment confirms ALT and/or AST $>5 \times$ ULN, 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 Appendix 1).
- If repeat LFT assessment confirms ALT and/or AST $>3 \times$ ULN in addition to any of the following, the patient should be given no further IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1):
 - TB $>2 \times$ ULN

Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of $2 \times$ ULN will be based upon direct (conjugated) bilirubin.

 - INR $>1.5 \times$ 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

New Text:

- If repeat LFT assessment confirms ALT and/or AST $>5 \times$ ULN, 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 Appendix 1) ***or more frequently as determined by the investigator.***
- If repeat LFT assessment confirms ALT and/or AST $>3 \times$ ULN in addition to any of the following, the patient should be given no further IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1) ***or more frequently as determined by the investigator:***
 - TB $>2 \times$ ULN

Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of $2 \times$ ULN will be based upon direct (conjugated) bilirubin.

 - INR $>1.5 \times$ 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

CHANGE 28 ASSESSMENT OF safety revisions

Location:

Section 11.1.6.3.4, Monitoring and Management of Elevated Creatine Kinase

Original Text:

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, if asymptomatic the investigator with input from the Sponsor may consider continuing study medication with continued CK assessments every 1-2 weeks.
- If symptomatic, the following steps should be completed:
 - Hold IMP
 - Clarification of the nature, duration, and intensity of muscle symptoms

New Text:

If at any time after randomization a patient experiences a marked CK elevation $>5 \times \text{ULN}$, 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 $>5 \times \text{ULN}$, if asymptomatic ~~the investigator with input from the Sponsor may consider continuing~~ ***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 and study-supplied ezetimibe should be discontinued*** ~~study medication with continued CK assessments every 1-2 weeks.~~
- If symptomatic, the following steps should be completed:
 - Hold IMP ***and study-supplied ezetimibe***
 - Clarification of the nature, duration, and intensity of muscle symptoms

CHANGE 29 ASSESSMENT OF SAFETY

Location:

Section 11.1.6.6, Collection and Assessment of Pharmacokinetic Samples

Original Text:

Pharmacokinetic samples will be collected from patients prior to the first dose at Week 0 (Visit T1), Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4), dosing time and PK sampling time must be documented, for use in further developing the population PK model.

Plasma concentrations of ETC-1002 and its metabolite (ESP15228) will be determined using validated methods. Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, "Plasma PK"). See the study laboratory manual for further instructions.

New Text:

Pharmacokinetic samples will be collected from patients prior to the first dose at ~~Week 0 (Visit T1)~~, Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4), dosing time and PK sampling time must be documented, for use in further developing the population PK model.

Plasma concentrations of ETC-1002 and its metabolite (ESP15228) will be determined using validated methods. Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, "Plasma PK"). See the study laboratory manual for further instructions.

CHANGE 30 ASSESSMENT OF SAFETY -- EXPLORATORY BIOMARKER MEASUREMENT REVISIONS

Location:

Section 11.1.6.7, Exploratory Biomarker Measurement

Original Text:

11.1.6.7 Exploratory Biomarker Measurement

Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from 10 mL blood samples reserved for potential future measurement of potential biomarkers.

New Text:

~~11.1.6.7 Exploratory Biomarker Measurement~~

~~Additional exploratory safety, efficacy, PK, or potential biomarkers may be assayed from 10 mL blood samples reserved for potential future measurement of potential biomarkers.~~

CHANGE 31 ASSESSMENT OF SAFETY – GENETIC TESTING REVISIONS

Location:

Section 11.1.6.9, Genetic Testing

Original Text:

11.1.6.9 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, but participation in this portion of the study is optional and where is approved by the IRB/IEC and by local law. 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. Signing a separate informed consent document is required to obtain this sample.

New Text:

~~11.1.6.9 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, but participation in this portion of the study is optional and where is approved by the IRB/IEC and by local law. 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. Signing a separate informed consent document is required to obtain this sample.~~

CHANGE 32 ASSESSMENT OF SAFETY – ADVERSE EVENTS REVISIONS

Location:

Section 11.2.3, 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 **through 30 days following the last dose of IMP** to the investigator. ***Any SAE that occurs within 30 days following the last study visit should be reported to the Sponsor per Section 11.3.*** 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.

CHANGE 33 ASSESSMENT OF SAFETY – ADVERSE EVENTS REVISIONS

Location:

Section 11.2.5, Relationship

Original Text:

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:

New Text:

It is the investigator's responsibility to assess the relationship *of the AE with* ~~between both the study drug IMP and ezetimibe and the AE~~. The degree of "relatedness" of the AE to the study drug *IMP and ezetimibe should* ~~may~~ be described using the following scale:

CHANGE 34 ASSESSMENT OF SAFETY –ADVERSE EVENTS REVISIONS

Location:

Section 11.2.7.1, Definition of Serious Adverse Event

Original Text:

Any clinical endpoints that meet SAE criteria will be also 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.

11.3. Reporting Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following study completion (for most patients 30 days following their Week 12 visit) or study discontinuation, must be reported by the principal investigator or designee to the authorized 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.

New Text:

Any clinical endpoints that meet SAE criteria will be also 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.

11.2.7.2 *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***

11.2.7.3 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 local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

11.3. Reporting Serious Adverse Events

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following ~~study completion~~ **last dose of IMP** (for most patients 30 days following their Week 12 visit) ~~or study discontinuation~~, must be reported by the principal investigator or designee to the authorized 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.

CHANGE 35 STATISTICS REVISIONS

Location:

Section 12.5, Primary Efficacy Analysis

Original Text:

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 as a factor 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 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 treatment as a factor 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 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.

New Text:

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

Baseline **LDC-C** 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 as a factor 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 correct for unequal variances and group size will be described in the SAP.***

~~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~~ ***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. Imputed datasets will be analyzed using ANCOVA with treatment as a factor 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 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. ***A confirmatory analysis using observed data only will also be performed for the primary endpoint.***

CHANGE 36 STATISTICS REVISIONS

Location:

Synopsis; Section 12.6, Secondary and Tertiary Efficacy Endpoints

Original Text:

For the remaining secondary efficacy endpoints (percent change from baseline to Week 12 in TG and HDL-C) and the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints (Section 5.4.3), the p-values for those endpoints will be considered descriptive.

Change from baseline to Week 12 in LDL-C and percent change from baseline to Week 12 in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA with treatment group as a factor and the relevant baseline as the covariate. Baseline for non-HDL-C, HDL-C, TC, and TG 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 (no imputation will be performed for missing data). For each lipid parameter at each 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-HDL-C, TC, TG, apoB, and hs-CRP, change from baseline in LDL-C; percent change and change from baseline in lipid levels to Weeks 4, 8, and 12, 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.

New Text:

For the remaining secondary efficacy endpoints (percent change from baseline to Week 12 in TG and HDL-C) and the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints (~~Section 5.4.3~~), the p-values for those endpoints will be considered descriptive.

~~Change from baseline to Week 12 in LDL-C and~~ ***In general, change or percent change from baseline to Week 12 in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP in lipid parameters at a given time point*** will each be analyzed using a ***similar ANCOVA model for the primary endpoint*** with treatment group as a factor and the relevant baseline as the covariate. Baseline for non-HDL-C, HDL-C, TC, and TG 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 (no imputation will be performed for missing data.~~ ***Same imputation method described for the primary endpoint will be used for the key secondary endpoints, while only observed data analysis will be used for other secondary and tertiary endpoints.*** For each lipid parameter at each 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-HDL-C, TC, TG, apoB, and hs-CRP, change from baseline in LDL-C; percent change and change from baseline in lipid levels to Weeks 4, 8, and 12, as appropriate), the~~ ***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 ***considered*** instead of the planned ANCOVA.

**CHANGE 37 APPENDIX 1 SCHEDULE OF EVENTS (PATIENT VISIT SCHEDULE)
REVISIONS**

Location:

Appendix 1, Schedule of Events (Patient Visit Schedule)

Original Text:

Visit	S1 ¹	S2	S3	T1	T2	T3	T4
Week	-5	-4	-1	0	4	8	12/EOS
Procedure	Day -42 to -35	Day -28 ± 3	Day -7 ± 3	Day 1	Day 29 ± 3	Day 57 ± 3	Day 85 ± 3
Informed Consent	X						
Enrollment Criteria	X	X	X	X			

Visit	S1 ¹	S2	S3	T1	T2	T3	T4
Week	-5	-4	-1	0	4	8	12/EOS
Procedure	Day -42 to -35	Day -28 ± 3	Day -7 ± 3	Day 1	Day 29 ± 3	Day 57 ± 3	Day 85 ± 3
Demographics	X						
Medical History	X						
Concomitant/Prohibited Medications	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X
Physical Exam		X					X
Weight ³	X			X ³			X
Height/BMI	X						
12-Lead ECG ⁴		X					X
Vital Signs ⁵	X	X	X	X	X	X	X
Serology ⁶		X					
Serum Pregnancy/FSH ⁷	X						
Urine Pregnancy				X			
TSH	X						
Clinical Safety Labs ⁸	X			X	X	X	X
Basic Fasting Lipids ⁹	X		X	X	X	X	X
Special Fasting Lipids and Other Biomarkers ¹⁰				X			X
HbA _{1C}	X			X			X
PK sample				X predose	X	X	X
Diet and exercise counseling	X	X	X	X	X	X	X
Randomization				X			
Single Blind/Ezetimibe Drug Dispensing		X		X ¹¹			
Double Blind Drug Dispensing				X			
Drug Return			X	X	X	X	X

BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone, HbA_{1C} = hepatitis B surface antigen; PK = pharmacokinetics; TSH = thyroid-stimulating hormone.

¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of the LDL values, or repeat TG value, will be used to determine eligibility.

² All procedures will be completed at end of study or early termination.

³ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

⁴ Single 12-lead ECG will be collected prior to any blood sample collection.

- ⁵ Vital signs will include SBP, DBP, and HR, and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.
- ⁶ Serology for Hep B antigen, Hep C antibody.
- ⁷ FSH completed in appropriate postmenopausal women only; pregnancy test completed in non-postmenopausal women only.
- ⁸ Clinical safety labs include hematology, blood chemistry, and urinalysis. Coagulation panel at S1 only, unless receiving anticoagulants (then test at T1 and repeat 3-5 days after starting IMP).
- ⁹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides.
- ¹⁰ Includes apoB and hs-CRP.
- ¹¹ Ezetimibe dispensing only.

New Text:

Visit	S1 ¹	S2	S3	T1	T2	T3	T4 ²
Week	-5	-4	-1	0	4	8	12/EOS
Procedure	Day -42 to -35 ±7 days	Day -28 ± 3	Day -7 ± 3	Day 1	Day 29 ± 3	Day 57 ± 3	Day 85 ± 3
Informed Consent	X						
Enrollment Criteria	X	X	X	X			
Demographics	X						
Medical History	X						
Concomitant/Prohibited Medications	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X
Physical Exam		X					X
Weight ³	X			X ³			X
Height/BMI	X						
12-Lead ECG ⁴		X					X
Vital Signs ⁵	X	X	X	X	X	X	X
Serology ⁶		X					
Serum Pregnancy/FSH ⁷	X						
Urine Pregnancy ⁷				X			
TSH	X						
Clinical Safety Labs ⁸	X		X	X	X	X	X
Basic Fasting Lipids ⁹	X		X	X	X	X	X
Special Fasting Lipids and Other Biomarkers ¹⁰				X			X
HbA _{1C}	X			X			X

Visit	S1 ¹	S2	S3	T1	T2	T3	T4 ²
Week	-5	-4	-1	0	4	8	12/EOS
Procedure	Day -42 to -35 ±7 days	Day -28 ± 3	Day -7 ± 3	Day 1	Day 29 ± 3	Day 57 ± 3	Day 85 ± 3
PK sample (<i>prior to IMP dosing</i>)				X predose	X	X	X
Diet and exercise counseling	X	X	X	X	X	X	X
Randomization				X			
Single Blind/Ezetimibe Drug Dispensing		X		X ¹¹			
Double Blind Drug Dispensing				X			
Drug Return ¹²			X	X	X	X	X

BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone, HbA_{1C} = hepatitis B surface antigen; PK = pharmacokinetics; TSH = thyroid-stimulating hormone.

¹ An optional visit approximately 1 week later MAY be completed if patient fails to meet **TG** lipid entry criterion. If this optional visit is completed, the ~~mean of the LDL values~~, or repeat TG value, will be used to determine eligibility.

² All procedures will be completed at end of study or early termination.

³ Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

⁴ Single 12-lead ECG will be collected prior to any blood sample collection.

⁵ Vital signs will include SBP, DBP, and HR, and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments.

⁶ Serology for Hep B antigen, Hep C antibody.

⁷ FSH completed in appropriate postmenopausal women only; pregnancy test completed in non-postmenopausal women only.

⁸ Clinical safety labs include hematology, blood chemistry, and urinalysis. Coagulation panel at S1 only, unless receiving anticoagulants (then test at T1 and repeat 3-5 days after starting IMP). ***For patients not taking ezetimibe at S1, measure blood chemistry and CK only at S3.***

⁹ Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides.

¹⁰ Includes apoB and hs-CRP.

¹¹ Ezetimibe dispensing only.

¹² ***Record unused IMP and ezetimibe and reissue study drug bottles at visits T1 (ezetimibe only), T2, and T3. Perform final drug count at visit T4.***

CHANGE 38 APPENDIX 2 SPONSOR'S SIGNATURE REVISIONS

Location:

Appendix 2, Sponsor's Signature (all pages within Appendix 2)

Original Text:

SPONSOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C

Study Number: 1002-048

New Text:

SPONSOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C *on Low Dose or Less than Low Dose Statins*

Study Number: 1002-048

CHANGE 39 APPENDIX 3 INVESTIGATOR'S SIGNATURE REVISIONS

Location:

Appendix 3, Investigator's Signature

Original Text:

INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C

Study Number: 1002-048

New Text:

INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C *on Low Dose or Less than Low Dose Statins*

Study Number: 1002-048