BEMPEDOIC ACID

1002-047

A LONG-TERM, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY OF BEMPEDOIC ACID (ETC-1002) IN PATIENTS WITH HYPERLIPIDEMIA AT HIGH CARDIOVASCULAR RISK NOT ADEQUATELY CONTROLLED BY THEIR LIPID-MODIFYING THERAPY

Study Phase:	3
IND Number:	106654
EudraCT Number:	2016-003486-26
Indication:	Treatment of hyperlipidemia
Investigators:	Approximately 125 sites located in the North America and Europe
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

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Original Protocol:	22 September 2016
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NCT number: NCT02991118
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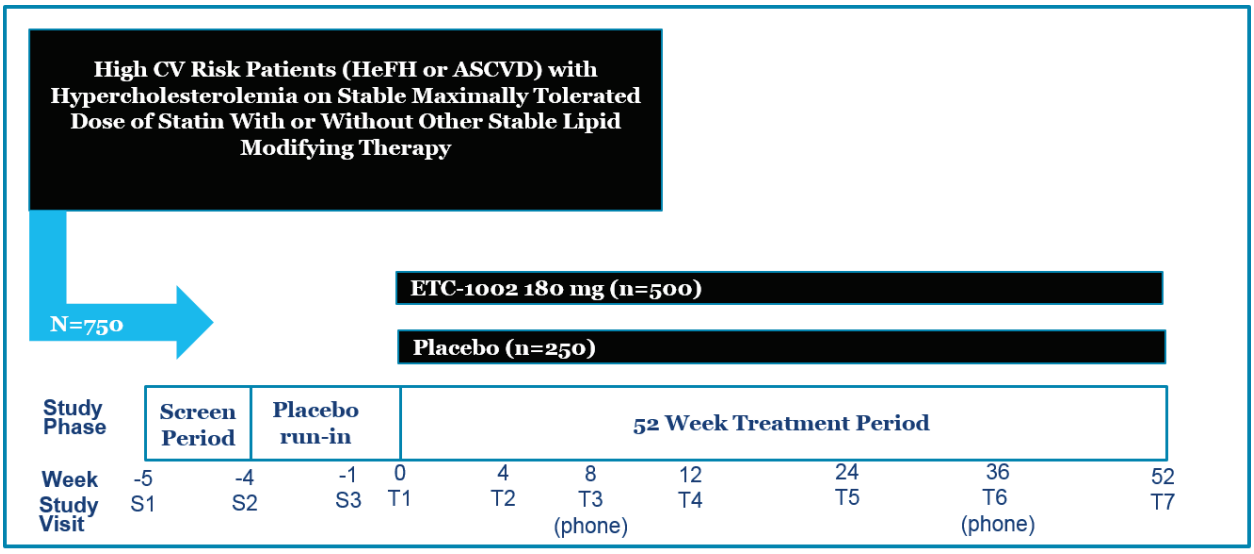
for purposes of posting on clinicaltrials.gov

2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.
Name of Investigational Product: Bempedoic Acid (ETC-1002) [redacted] tablets
Name of Active Ingredient: Bempedoic acid (ETC-1002)
Title of Study: A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy
Study Number: 1002-047
Phase of Development: 3
Clinical Sites: Approximately 125 sites located in North America and Europe
Objectives: **Primary:** • To assess the 12-week efficacy of bempedoic acid (ETC-1002) 180 mg/day versus placebo in decreasing low-density lipoprotein cholesterol (LDL-C) in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy. **Secondary:** • To evaluate the effect of 24-week treatment with bempedoic acid 180 mg/day versus placebo on LDL-C. • To evaluate the effect of bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-sensitivity C-reactive protein (hs-CRP), and apolipoprotein B (apoB) after 12 weeks of treatment. **Tertiary:** • To evaluate the effect of long-term (52-week) treatment with bempedoic acid 180 mg/day versus placebo on LDL-C, non-HDL-C, TC, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), hs-CRP, and apoB. • To evaluate the long-term (52-week) safety and tolerability of bempedoic acid 180 mg/day compared to placebo.

Methodology:

1002-047 STUDY DESIGN



Study Design:

This is a Phase 3, long-term, randomized, double-blind, placebo-controlled, parallel group, study evaluating the efficacy of bempedoic acid in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-modifying therapy includes a maximally tolerated statin alone or in combination with other lipid-modifying therapies (eg, ezetimibe, fibrates [except gemfibrozil, as per co-administration instructions defined in the statin label], and proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors). Maximally tolerated statin includes statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must be documented. A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Screening Week -5 (Visit S1) will be approximately 5 weeks prior to randomization, but can be extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons as specified in the protocol. Eligible patients will return to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence. Patients must be 80% compliant with placebo during run-in to be eligible. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel regarding their eligibility status and considered screen failures. As necessary, for reasons of safety if a patient begins the run-in period but screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of adverse events (AEs).

Patients on maximally tolerated lipid-modifying therapy, as determined by the investigator, will be stratified based on the patient's CV risk (ASCVD alone; HeFH with or without ASCVD) and baseline statin intensity (high intensity statin; moderate intensity statin; low intensity statin), for a total of 6 strata. Statin intensity categories are defined below in the table:

High Intensity Statins[a]	Moderate Intensity Statins	Low Intensity Statins[b]
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

[a] Simvastatin doses ≥40 mg/day are not allowed.

[b] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and those unable to tolerate a statin at any dose

Thus, the randomization stratum for this study are:

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH + Low Intensity Statins[a]	ASCVD + Low Intensity Statins[a]
HeFH + Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH + High Intensity Statins	ASCVD + High Intensity Statins

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

[a] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and those unable to tolerate a statin at any dose

Approximately 750 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = 500), or placebo (n = 250) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (T6). Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see the Schedule of Events in Appendix 1.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction [MI] (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.

Primary Endpoint

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

Secondary Endpoints

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

Tertiary Endpoints

1. Absolute change and percent change from baseline to Week 52 in LDL-C
2. Percent change from baseline to Weeks 24 and 52 in non-HDL-C, TC, apoB, and hs-CRP
3. Percent change from baseline to Weeks 12, 24, and 52 in TG and HDL-C

Safety Endpoints

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

Number of patients (planned): Approximately 750 adult male and female patients

Duration of treatment: All patients will be treated for 52 weeks

End of Study: The study will end when the last randomized patient completes the Week 52 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 21 months.

Diagnosis and criteria for patient eligibility:

The study will enroll adult male and female patients with hyperlipidemia

Each patient must meet the following criteria to be eligible for this study:

Inclusion Criteria

1. Provision of written informed consent prior to any study-specific procedure
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Week -5 (Visit S1)
3. Men and nonpregnant, nonlactating women.
4. Women must be either:
   - Naturally postmenopausal (as reported by the patient, defined as greater than 55 years and ≥1 year without menses, <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L), or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential must be willing to use 2 acceptable methods of birth control (unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include: oral, implantable, injectable, or topical birth control medications; placement of an intrauterine device (IUD) 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; or 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 the trial, and withdrawal are not acceptable methods of contraception).

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

5. Fasting LDL-C (minimum of 10 hours) value at Week -5 (Visit S1) ≥100 mg/dL (2.6 mmol/L) and fasting LDL-C value at Week -1 (Visit S3) ≥70 mg/dL (1.8 mmol/L)
6. Have high CV risk that is defined as either:
   - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established coronary heart disease (CHD) or CHD risk equivalents.

     OR
   - Have ASCVD (with established CHD or CHD risk equivalents)

     Documented history of CHD (includes 1 or more of the following):
     - Acute MI
     - Silent MI
     - Unstable angina
     - Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)
     - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging)

     Documented CHD risk equivalents (includes 1 or more of the following criteria):
     - Symptomatic peripheral arterial disease (PAD) defined as
       - peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 performed by a vascular lab or
       - angiogram (including computed tomographic angiography [CTA]) showing ≥50% stenosis or
       - peripheral arterial revascularization (surgical or percutaneous) occurring greater than 90 days prior to Visit S1 or
       - abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair occurring greater than 90 days prior to Visit S1 or
       - lower extremity amputation due to peripheral vascular disease occurring greater than 90 days prior to Visit S1
     - Cerebrovascular atherosclerotic disease defined by:
       - ischemic stroke occurring greater than 90 days prior to Visit S1 or
       - Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram occurring greater than 90 days prior to Visit S1.

       Note: Patients with T2DM are allowed in this study; however, for this study T2DM is not considered a CHD risk equivalent
7. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin either alone or in combination with other lipid-modifying therapies, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed as per co-administration instructions defined in the statin label). Maximally tolerated statin includes statin

regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must be documented.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Note: Patients can be on any available lipid-modifying therapy with the exception of the exclusions listed below as long as they have been stable for 4 weeks prior to Screening Visit S1 and are taken at a consistent time each day. In the case of PCSK9 inhibitor use, the patient must have received 3 stable doses. It is important that lipid values are measured at PCSK9i trough levels. Therefore, study visits should be scheduled in accordance with the patient's PCSK9i injection regimen so that measurement of lipid values for all visits occurs before the PCSK9i injection but not greater than 48 hours before the next scheduled PCSK9i injection. Patients who have discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least 4 months prior to Screening Visit S1.

Exclusion Criteria:

1. 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 between Visits S1 and S2. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.
2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Week -5 (Visit S1) (Levey 2006).

   Note: At the discretion of the investigator, the screening period may be extended up to 4 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value should be obtained between Visits S1 and S2 and will be used to determine eligibility.
3. Body mass index (BMI) ≥50 kg/m^2
4. Recent (within 3 months prior to the screening visit [Week -5 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.
5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg 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 (between Visits S1 and S2) 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.
6. Hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -5 (Visit S1)
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.
8. Liver disease or dysfunction, including:

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

  Note: At the discretion of the investigator, a single repeat of ALT 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 reflexive test for Hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.

9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption
10. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL (100 g/L) 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 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients 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, blood transfusion, participation in a clinical study with multiple blood draws, major trauma, 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.
16. Previous enrollment in a bempedoic acid clinical study.
17. Use of any of the following drugs or a plan to use these drugs during the study:
    - New or planned dose changes of systemic corticosteroids. Stable doses (≥4 weeks before Visit S1) and topical corticosteroids allowed.
    - CETP inhibitors within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months prior to screening (Week -5, Visit S1)
    - Mipomersen (6 months prior to screening, Week -5, Visit S1)
    - Lomitapide (3 months prior to screening, Week -5, Visit S1)
    - Apheresis (3 months prior to screening, Week -5, Visit S1)
    - Simvastatin ≥40 mg/day (4 weeks prior to screening, Week -5, Visit S1)
    - Red yeast rice extract -containing products are not allowed (2 weeks prior to screening, Week -5, Visit S1)
18. Planned initiation of the following drugs during the clinical trial or changes prior to randomization (Day 1, Visit T1):
    - Hormone replacement (6 weeks prior to randomization)
    - Thyroid replacement (6 weeks prior to randomization)
    - Diabetes medications (4 weeks prior to randomization)
    - Obesity medication (4 weeks prior to randomization)

19. Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
20. Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
21. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
23. Pregnant, breastfeeding, or intending to become pregnant within 30 days after last dose of study drug.
24. Patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9 are excluded.

IMP, dosage and mode of administration:

- Bempedoic acid 180-mg tablets.
- Matching placebo tablets
- All IMP will be ingested once daily with or without food.

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

- Background lipid-lowering therapy including maximally tolerated statins
- All background lipid-lowering therapy will be ingested as prescribed by a physician

Criteria for evaluation:

Lipid Assessments:

- Calculated LDL-C, HDL-C, non-HDL-C, TC, apoB, 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.

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 as appropriate. Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, coagulation, HbA_{1C}, fasting glucose, and urinalysis), physical examination (PE) findings, vital signs, electrocardiogram (ECG) readings, and weight.

Clinical Laboratory Assessments:

- Hematology: Hematocrit (Hct), Hgb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute values only)
- Urinalysis (Dipstick): Clarity, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen
- Urinalysis (Microscopic): Obtain centrally only if positive urine dipstick; bacteria, casts, crystals, epithelial cells, RBC, and WBC
- Coagulation: Prothrombin time (PT), 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 (CO_2), chloride (Cl), creatinine, CK, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid
- HbA_{1C}

Other Screening Laboratories:

- HBsAg, hepatitis C virus (HCV), serum pregnancy test (only for females who are of childbearing potential), FSH (only for females who are <55 years old and >1 year without menses), urine

pregnancy test (for females of childbearing potential) on Day 1 prior to randomization, TSH

PK and other Biomarkers:

- hs-CRP
- Plasma PK concentrations will be collected prior to dose at Weeks 24 and 52, for use in further developing the population pharmacokinetic (PK) model.

Safety and Monitoring:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and ≥25% from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
  - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
  - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at doses ≥40 mg/day and the fibrate gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).
  - The initiation of any new or dose changes of any lipid-lowering treatment will be documented on the electronic case report form (eCRF) as a concomitant medication with the associated start date
  - Patients who have their lipid-lowering treatments modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion.
  - Adjunctive therapy medications will not be provided by the sponsor
  - Patients continuing to exceed the LDL-C threshold after maximizing the standard-of-care LDL-C-lowering therapy and, in the opinion of the investigator, require therapies that are prohibited by the protocol will be discontinued from IMP treatment and will be asked to continue to be followed for safety using the protocol-specified visit schedule.

Monitoring and Management Plans for Triglyceride Elevations:

Elevated Triglycerides:

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

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

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

Adverse Events Associated with Experience with Bempedoic Acid to Date:

Potential AEs:

Based on findings in nonclinical models, potential AEs include reversible hypoglycemia and metabolic acidosis. Patients will be educated on the signs and symptoms of hypoglycemia and asked to report the experienced signs and symptoms to the investigator. Investigator confirmed occurrences of hypoglycemia will be reported as AEs. 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 glucose will also be evaluated across treatment groups during this study and all ongoing studies to identify potential cases of new onset of diabetes

Neurocognitive Events:

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

Clinical Endpoints:

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

Routine cardiovascular monitoring will include review of cardiovascular AEs, SAEs, (both as adjudicated by the CEC), standard vital signs, and ECGs.

Additional details regarding safety monitoring are included in Section 11.1.6.3.1 through Section 11.1.6.4.

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

Statistical methods:

Sample Size

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

The sample size of 500 randomized patients in the bempedoic acid 180 mg group and 250 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 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 ($\alpha = 0.05$) and a common standard deviation of 15%. The sample size of 500 randomized patients in the bempedoic acid 180 mg group and 250 randomized patients in the placebo group gives a total study

sample size of 750.

Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy summaries and 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 Endpoint

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a covariate. Baseline LDL-C is defined as the mean of the LDL-C values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). The primary analysis will be that from the PMM, while the observed case analysis will be used as confirmatory. The PMM will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Imputed datasets will be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a covariate. Approximately 200 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

Secondary and Tertiary Efficacy Endpoints

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

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

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

Percent change from baseline to Week 24 in LDL-C; absolute change from baseline to Weeks 12, 24,

and 52 in LDL-C; percent change from baseline to Weeks 12, 24, and 52 in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and the relevant baseline as a covariate. Baseline for HDL-C, non-HDL-C, TG, and TC will be defined as the mean of the lipid values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the lipid values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP will be defined as the predose Day 1/Week 0 (Visit T1) value. Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. For each lipid parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For all continuous efficacy endpoints (percent change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP; change from baseline in LDL-C; to Weeks 12, 24, and 52, 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.

In addition, a summary of percent change from baseline to Week 12 LDL-C using the FAS, excluding patients who received additional lipid-lowering therapy by that time point (by Week 12 for the Week 12 time point), will be provided. Percent change from baseline to Weeks 24 and 52 on LDL-C will be analyzed similarly, with patients in the FAS who did not receive additional LDL or triglyceride-lowering therapy by that time point (by Week 24 for the Week 24 analysis by Week 52 for the Week 52 analysis) included in the analyses. Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI, and p-value.

Additional post-randomization adjunctive lipid-modifying therapy

The number and percent of patients in each treatment group requiring additional (post-randomization) adjunctive lipid-modifying therapy will be summarized. Medications and the reasons for their additional treatment (hyperlipidemia vs. hypertriglyceridemia) will be summarized separately.

Safety Analyses

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

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

Hepatic Safety

Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST, and TB. Hy's law criteria ($\geq 3 \times$ ULN for either ALT or AST, with accompanying TB $>2 \times$ ULN or patient's baseline) will also be applied to the data; any potential Hy's law cases will be listed separately. In the case of patients with Gilbert's disease, TB will be fractionated and the determination of $2 \times$ ULN based upon direct (conjugated) bilirubin.

Musculoskeletal Safety

AEs of muscle-related symptoms will be summarized by treatment group. CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal CK values will be summarized. These summaries of patients with abnormal CK will be performed overall; by normal baseline CK; and by abnormal baseline CK.

Diabetes and Hyperglycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group. Glucose and HbA_{1C} will be monitored at baseline and at Weeks 12 and 24and be summarized.

Renal Safety

Baseline eGFR will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. 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 SOC, severity, and relationship to study drug for each 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 of ETC-1002 and its metabolite ESP15228 will be summarized prior to dose at Weeks 24 and 52.

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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	Area under the concentration-time curve
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
CEC	Clinical Event Committee
CETP	Cholesterol ester transfer protein
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
C_{max}	Time to peak maximum concentrations
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Acetyl-coenzyme A

Abbreviation or Specialist Term	Explanation
CO_2	Carbon dioxide
CRO	Contract research organization
CT	Computed tomography
CTA	Computed tomographic angiography
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
ETC-1002	Bempedoic acid
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
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

Abbreviation or Specialist Term	Explanation
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LPLV	Last patient last visit
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
NA	Not applicable
NIMP	Non-investigational medicinal product(s)
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PMM	Pattern mixed model

Abbreviation or Specialist Term	Explanation
PT	Prothrombin time
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SOP	Standard operating procedures
SP	Safety population
SUSARS	Suspected and unexpected serious adverse reactions
$t_{½}$	Terminal elimination half-live
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal
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.

Hyperlipidemic patients at high CV risk due to either heterozygous familial hypercholesterolemia (HeFH) and/or established atherosclerotic cardiovascular disease (ASCVD) unable to meet their LDL-C treatment goals with currently available therapies are the target patient populations for this study.

Elevated LDL-C is a major modifiable risk factor for the development of atherosclerosis and ASCVD (Sharrett 2001). Despite aggressive interventional and pharmacologic therapies, CV disease is the number 1 cause of death globally (WHO 2015). An estimated 17.5 million people died from CV diseases in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease (CHD) and 6.7 million were due to stroke (WHO 2015). Cardiovascular disease remains the leading cause of death among Europeans, Americans, and around the world. The Global Burden of Disease study estimated that 29.6% of all deaths worldwide (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 (Nichols 2014). 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 (Mozffarian 2015).

Patients with documented ASCVD are at very high risk for events and require intensive pharmacologic intervention (Stone 2014). For a variety of reasons, many with ASCVD are unable to attain aggressive LDL-C treatment goals despite the addition of lipid-lowering agents to maximally tolerated statin therapy (Jacobson 2014).

Familial hypercholesterolemia refers to individuals with extremely elevated LDL-C due to underlying genetic mutations of the LDL receptor (LDLR), apolipoprotein B (apoB), and proprotein convertase subtilisin/kexin type 9 (PCSK9) (FH Foundation 2015). In adult HeFH patients, LDL-C usually exceeds 190 mg/dL (4.9 mmol/L) and can be as high as 400 mg/dL (10.4 mmol/L). HeFH is the most common form of the disease with a prevalence of approximately 1 in 300 to 500 persons worldwide and as high as 1 in 100 persons in some populations (NORD 2015). Patients with HeFH inherit a genetic mutation from 1 parent. Inheritance is generally via an autosomal-dominant mechanism (Robinson 2013). HeFH increases the risk of atherosclerosis leading to CV events. The mean age for the onset of CV

disease is relatively young, at 42 to 46 years in men and 51 to 52 years in women (Robinson 2013). The cumulative risk of experiencing a coronary event by the age of 60 years without effective treatment is at least 50% in men and approximately 30% in women with a marked increase in postmenopausal women. Before effective treatment with statins became available, mortality from coronary disease was increased by nearly 100-fold in young adults 20 to 39 years of age, and approximately 4-fold for patients aged 40 to 59 years (Neil 2008). The National Lipid Association (NLA) recommends achievement of ≥50% reduction in LDL-C in adult patients using statins. HeFH patients at even higher risk for CV disease (such as those with established ASCVD, diabetes, smoking, family history, and other risk factors) have a treatment goal of ≤70 mg/dL (1.8 mmol/L). Those unable to achieve these treatment goals with maximally tolerated statin therapy require additional lipid-lowering therapy and still may be unable to reach LDL-C treatment goals.

Lowering LDL-C is the primary therapeutic lipid target in ASCVD and HeFH patients (Goldberg 2011). LDL-C is largely accepted as a valid surrogate endpoint of CV events by clinicians and regulatory authorities (Stone 2014). 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 reduce plasma LDL-C by >15%. Particularly in ASCVD and HeFH patients, pharmacologic treatments are required to adequately treat hyperlipidemia (Pollex 2008). 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 (Kathiresan 2008; Baigent 2010; Robinson 2005; Stamler 1986). 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 (Baigent 2010). This analysis showed that with a 1 mmol/L reduction in LDL-C 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 (Cannon 2004). Unfortunately, some patients are unable to take high intensity statins due to dosing limits based on co-morbidities, contraindications, and/or tolerance (Jacobson 2014). Nonstatin therapies may provide additional lowering of CV risk as demonstrated in the IMPROVE-IT trial which added ezetimibe to statin therapy (Cannon 2015).

Patients with ASCVD and HeFH on maximally tolerated lipid-lowering therapy including maximally tolerated doses of statins who require additional lipid-lowering therapy have an unmet medical need. ETC-1002 may offer a once daily option for these patients. The oral route of administration may be preferable to injectable biologic therapy for some patients. 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-co-enzyme A (ETC-1002-CoA), which mediates competitive inhibition of ACL. Inhibition of ACL by ETC-1002-CoA decreases cholesterol synthesis in liver leading to increased LDLR expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002-CoA reduces LDL-C via the same pathway as HMG-CoA reductase inhibition by statins.

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

4.2.2. Nonclinical Experience

The primary pharmacology of bempedoic acid was evaluated in several well-characterized and predictive rodent models of dyslipidemia. In these studies, bempedoic acid lowered LDL-C and triglycerides (TGs) and increased high-density lipoprotein cholesterol (HDL-C). In a study of cholesterol-fed LDLR-deficient mice, bempedoic acid substantially slowed the progression of atherosclerosis in a dose-related manner.

Results of the safety pharmacology studies did not identify any significant risks for subjects over the range of exposures intended for clinical studies.

In toxicology studies, evaluations of bempedoic acid in mice, rats, and monkeys in oral studies up to 52 weeks in duration have been completed. No significant central nervous system (CNS), respiratory, or CV liabilities were identified. Target organs identified in repeat-dose studies were liver in rats and liver and kidney in monkeys, and changes were reversible following cessation of treatment. Changes in clinical laboratory parameters indicative of hepatic and renal function were observed in animals at doses lower than those associated with frank toxicity. Routine clinical laboratory parameters will continue to be monitored carefully in clinical trials.

Bempedoic acid is nonmutagenic and nonclastogenic in both in vitro and in vivo genetic toxicology assays.

In the pivotal 26-week rat study, the no-observed-adverse-effect level (NOAEL) dose was 30 mg/kg/day in rats and the corresponding area under the curve during 24 hours (AUC_{0-24}) values of the sum of ETC-1002 and ESP15228 were up to 528 µg·hr/mL. In the pivotal 52-week monkey study, the NOAEL dose was 60 mg/kg/day and the corresponding AUC_{0-24} values of the sum of ETC-1002 and ESP15228 were up to 4760 µg·hr/mL.

In vitro studies indicated that bempedoic acid is neither an inhibitor nor inducer of major cytochrome P450 (CYP) enzymes at clinically relevant plasma concentrations. In addition, ETC-1002 bempedoic acid does not appear to inhibit major drug transporters.

Please refer to the most recent Investigator's Brochure (IB) for additional information regarding pharmacology, pharmacokinetics (PK), and nonclinical safety studies.

4.2.3. Previous Human Experience

Bempedoic acid has been evaluated in 15 completed clinical studies (nine Phase 1 and six Phase 2), with over 700 subjects receiving bempedoic acid doses from 2.5 mg/day up to 240 mg/day (multiple doses) for up to 12 weeks. All multiple-dose studies have demonstrated consistent, clinically meaningful LDL-C lowering with bempedoic acid treatment and have shown a positive safety profile. This efficacy was observed across a range of patient populations, including those with primary hyperlipidemia and mixed dyslipidemia, some of whom also reported type 2 diabetes mellitus (T2DM), CHD, and/or statin intolerance. In addition, a positive benefit/risk profile is shown across a range of low and moderate dose statins and ezetimibe.

In both single- and multiple-dose studies, bempedoic acid is well absorbed (with a time to peak maximum concentration [C_{max}] of approximately <4 hours). The C_{max} of ETC-1002 and ESP15228 increased in proportion to increasing dose; and the area under the concentration-time curve (AUC) showed slightly more than dose-proportional increases for ETC-1002 with increasing dose, but proportional increases in AUC were observed with ESP15228. The terminal elimination half-life ($t_{½}$) ranged from 15 to 27 hours for ETC-1002 and 20 to 33 hours for ESP15228.

A study to assess the effect of a high-fat, high-calorie meal on the bioavailability of ETC-1002 following administration of 180-mg tablet relative to the fasted state, the bioavailability of 180-mg capsules relative to one 180-mg tablet in the fasted state, and the bioavailability of three 60-mg tablets relative to one 180-mg tablet has completed (1002-016). A high-fat meal has no effect on the PK of ETC-1002 180-mg tablet; ETC-1002 PK are equivalent whether taken in the fasting or fed state. The evaluation of the tablet formulation that will be used in Phase 3 demonstrates similar PK characteristics to the capsule formulation utilized in Phases 1 and 2. The PK following three 60-mg tablets was similar to one 180-mg tablet. Only the 180-mg tablet is planned for use in Phase 3.

Two studies evaluated clinical drug-drug interaction using bempedoic acid 240 mg and showed less than a 2-fold increase in the exposure of atorvastatin 10 mg, simvastatin 20 mg, pravastatin 40 mg, and rosuvastatin 10 mg (Studies 1002-007 and 1002-012). Likewise, when bempedoic acid 180 mg was dosed in combination with high-dose statins (atorvastatin 80 mg, pravastatin 80 mg, rosuvastatin 40 mg, and simvastatin 40 mg), mean exposure of these statins increased between approximately 1.4- and 2-fold (1002-037).

No drug interaction occurred between daily ETC-1002 180 mg and metformin in patients with T2DM. A Phase 2 study showed no effect of ezetimibe 10 mg on steady-state trough ETC-1002 plasma concentrations in 40 patients with hypercholesterolemia randomized to receive ETC-1002 plus ezetimibe (Study 1002-008). Results of a drug interaction study in 19 patients (16 evaluable for PK) with the oral contraceptive Ortho-Novum 1/35 in healthy women demonstrate no effect of daily ETC-1002 180 mg on ethinyl estradiol or norethindrone exposure (Study 1002-017).

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

Occurrences of treatment-emergent adverse events (TEAEs), withdrawals due to adverse events (AEs), and treatment-related AEs were similar across groups receiving bempedoic acid, placebo or an active comparator, ezetimibe. Across the 15 clinical studies, the most frequently reported TEAEs included musculoskeletal and connective tissue disorders (back pain, pain in extremity, myalgia, arthralgia, muscle spasms), nervous system disorders (headache), gastrointestinal (GI) disorders (nausea, diarrhea), and infections and infestations. Overall, AEs were generally reported with similar incidence between treatment groups; however, the incidence of headache was higher with bempedoic acid than placebo. AEs were typically characterized as mild or moderate. Treatment-emergent serious adverse events (SAEs) were reported for 11 subjects. There has been 1 death: an event of sudden death (cause unknown) in a bempedoic acid-treated subject in Clinical Study 1002-008. The event was assessed by the investigator as severe and as possibly related to study treatment. The rationale for the investigator assessment was that a relationship to bempedoic acid could not be ruled out given the temporal nature of the event. A full narrative for this event is presented in the IB.

In general, laboratory results showed no clinically significant trends.

4.2.4. Dose Selection

Doses of bempedoic acid ranging from 40 to 240 mg/day have been evaluated in the Phase 2 program. Based on data from the integrated analysis of safety and efficacy, observed values and percent change from baseline in the primary efficacy endpoint, LDL-C together with a positive safety profile, support the choice of the 180-mg dose for the Phase 3 studies. An integrated analysis of six Phase 2 studies resulted in placebo-adjusted least square (LS) means for percent change from baseline of approximately 32% with bempedoic acid 180 mg monotherapy, 50% with bempedoic acid 180 mg + ezetimibe 10 mg, and 22% for 180 mg on top of stable statin therapy. The 180-mg dose was noted to have an excellent safety profile. Overall, balancing efficacy and safety the 180-mg dose was chosen for the Phase 3 program.

4.2.5. Background Therapy

Bempedoic acid in this study is currently being evaluated as an add-on to lipid-modifying therapy in high-risk patients (ie, those with HeFH and/or ASCVD) who have not achieved their LDL-C goal despite maximally tolerated lipid-modifying therapy.

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 Phase 3 studies.

Please refer to the most recent IB for additional information regarding previous human experience.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Study Objectives

5.1.1. Primary Objective

- To assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing LDL-C in high CV risk patients with hyperlipidemia (with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

5.1.2. Secondary Objectives

- To evaluate the effect of 24-week treatment with bempedoic acid 180 mg/day versus placebo on LDL-C.
- To evaluate the effect of bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-sensitivity C-reactive protein (hs-CRP), and apoB after 12 weeks of treatment.

5.1.3. Tertiary Objectives

- To evaluate the effect of long-term treatment (52 weeks) with bempedoic acid 180 mg/day versus placebo on LDL-C, non-HDL-C, TC, HDL-C, TG, hs-CRP, and apoB.
- To evaluate the long-term (52 weeks) safety and tolerability of bempedoic acid 180 mg/day compared to placebo.

5.2. Study Endpoints

5.2.1. Primary Endpoint

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

5.2.2. Secondary Endpoints

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

5.2.3. Tertiary Endpoints

Tertiary efficacy endpoints are of interest:

1. Absolute change and percent change from baseline to Week 52 in LDL-C

2. Percent change from baseline to Weeks 24 and 52 in non-HDL-C, TC, apoB, and hs-CRP
3. Percent change from baseline to Weeks 12, 24, and 52, in TG and HDL-C

5.2.4. Safety Endpoints

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

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 3, long-term randomized, double-blind, placebo-controlled, parallel group, study evaluating the efficacy of bempedoic acid in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-modifying therapy includes a maximally tolerated statin alone or in combination with other lipid-modifying therapies (eg, ezetimibe, fibrates [except gemfibrozil, as per co-administration instructions defined in the statin label] and PCSK9 inhibitors). A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

The study will be conducted at approximately 125 clinical sites in the North America and Europe.

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

Patients on maximally tolerated lipid-modifying therapy, as determined by the investigator, will be stratified based on the patient's CV risk (ASCVD alone; HeFH with or without ASCVD) and baseline statin intensity (high intensity statin, moderate intensity statin, low intensity statin) for a total of 6 strata. Statin intensity categories and randomization strata are defined in Table 2 and Table 3 below, respectively. Intensity category is based on average daily dose.

Table 2: Baseline Statin Dose Categories

High Intensity Statins[a]	Moderate Intensity Statins	Low Intensity Statins[b]
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

[a] Simvastatin doses ≥40 mg/day are not allowed.

[b] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and those unable to tolerate a statin at any dose.

Table 3: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH + Low Intensity Statins[a]	ASCVD + Low Intensity Statins[a]
HeFH + Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH + High Intensity Statins	ASCVD + High Intensity Statins

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

[a] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and those unable to tolerate a statin at any dose.

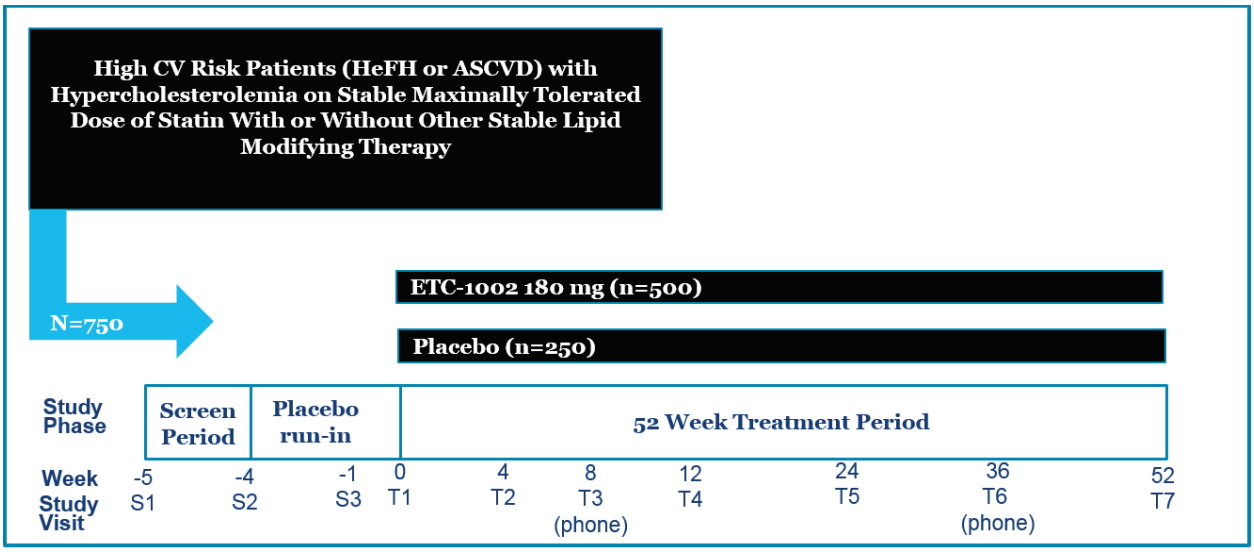
Approximately 750 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = 500), or placebo (n = 250) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (Visit T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (Visit T6).

Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule. For details of study assessments, see the Schedule of Events in Appendix 1.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: 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.

Figure 1. Study 1002-047 Study Design



6.2. Study Hypothesis

The study will assess the 12-week efficacy of bempedoic acid in decreasing LDL-C versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin alone or in combination with other lipid-lowering therapies, in patients with hyperlipidemia. The randomized, double-blind, placebo-controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that efficacy data are meaningful and interpretable. The treatment duration (52 weeks) and large patient number (n = 750) will provide robust long-term data on lipid profile, safety, and tolerability in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as bempedoic acid once daily, orally bioavailable option.

6.3. Study Duration and Period

The expected total duration of study participation for each randomized patient is approximately 57 weeks. The study will consist of an approximately 1-week screening period, a 4-week placebo run-in period, and a 52-week of treatment period.

6.4. End of Study

The study will end when the last randomized patient completes the Week 52 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 21 months.

6.5. Number of Patients

The study will enroll approximately 750 adult male and female HeFH and/or ASCVD patients with hyperlipidemia from approximately 125 clinical sites.

6.6. Patient Identification Numbers

A unique patient identification number will be assigned to each patient 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. Screening and Placebo Run-in Period

Screening will occur approximately 5 weeks prior to Day 1 (Visit T1) where the patient's eligibility will be evaluated. Eligible patients who are taking allowed concomitant medications must be on stable regimens as defined in Section 8.2. At the investigator's discretion, screening (time between visits S1 and S2) 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 single-blind (patient only) placebo. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence (see Section 7.1 and Section 7.2 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 screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of AEs.

6.6.1. Randomization and Treatment Period

For patients who satisfy all entry criteria and complete the 1-week screening period and 4-week run-in period, randomization will occur and their randomization number will be assigned via IWRS at Week 0 (Visit T1). Patients will be stratified on CV risk (HeFH and ASCVD diagnosis) and baseline statin intensity (high intensity statin, moderate intensity statin, low intensity statin), and randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- Bempedoic acid 180-mg tablet
- Matching placebo tablet

For details regarding the randomization strata see Table 3.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Subject Inclusion Criteria

Each patient with hyperlipidemia must meet the following criteria to be randomized in this 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. Men and nonpregnant, nonlactating women.
4. Women must be either:
   - Naturally postmenopausal (as reported by the patient, defined as greater than 55 years and ≥1 year without menses, <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L), or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential must be willing to use 2 acceptable methods of birth control (unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception it is that it 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 (IUD) 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; or 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 the trial, and withdrawal are not acceptable methods of contraception).

   There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
5. Fasting LDL-C (minimum of 10 hours) value at Week -5 (Visit S1) ≥100 mg/dL (2.6 mmol/L) and fasting LDL-C value at Week -1 (Visit S3) ≥70 mg/dL (1.8 mmol/L).
6. Have high CV risk that is defined as either:
   - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established CHD or CHD risk equivalents.

     OR

- Have ASCVD (with established CHD or CHD risk equivalents)

  Documented history of CHD (includes 1 or more of the following):

  – Acute MI

  – Silent MI

  – Unstable angina

  – Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)

  – Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

  Documented CHD risk equivalents (includes 1 or more of the following criteria):

  – Symptomatic peripheral arterial disease (PAD) defined as

    ○ Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 performed by a vascular lab or

    ○ Angiogram (including computed tomographic angiography [CTA]) showing ≥50% stenosis or

    ○ Peripheral arterial revascularization (surgical or percutaneous) occurring greater than 90 days prior to Visit S1 or

    ○ Lower extremity amputation due to peripheral vascular disease occurring greater than 90 days prior to Visit S1

  – Cerebrovascular atherosclerotic disease defined by:

    ○ ischemic stroke occurring greater than 90 days prior to Visit S1 or

    ○ Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram occurring greater than 90 days prior to Visit S1.

      Note: Patients with T2DM are allowed in this study; however, for this study T2DM is not considered a CHD risk equivalent

7. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin either alone or in combination with other lipid-lowering therapies, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed as per co-administration instructions defined in the statin label). Maximally tolerated statin includes statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must be documented.

   A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Note: Patients can be on any available lipid-modifying therapy with the exception of the exclusions listed below as long as they have been stable for 4 weeks prior to Screening Visit S1 and are taken at a consistent time each day. In the case of PCSK9 inhibitor use, the patient must have received 3 stable doses. It is important that lipid values are measured at PCSK9i trough levels. Therefore, study visits should be scheduled in accordance with the patient's PCSK9i injection regimen so that measurement of lipid values for all visits occurs before the PCSK9i injection but not greater than 48 hours before the next scheduled PCSK9 injection. Patients who have discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least 4 months prior to Screening Visit S1.

7.2. Subject Exclusion Criteria

Patients who meet any of the following criteria will not be randomized:

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

   Note: TG may be repeated 1 time between Visits S1 and S2. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73m^2 at Week -5 (Visit S1) (Levey 2006).

   Note: At the discretion of the investigator, the screening period may be extended up to 4 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value should be obtained between visits S1 and S2 and will be used to determine eligibility.

3. Body mass index (BMI) ≥50 kg/m^2

4. Recent (within 3 months prior to the screening visit [Week -5 (Visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.

5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg 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 (between Visits S1

and S2) 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.

6. Hemoglobin A_{1C} (HbA_{1C}) ≥10% at Week -5 (Visit S1)
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.
8. Liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -5 (Visit S1); or
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥1.2 × ULN at Week -5 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

   Note: At the discretion of the investigator, a single repeat of ALT 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 reflexive test for Hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption
10. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL (100 g/L) 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 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients 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, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, 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.
16. Previous enrollment in a bempedoic acid clinical study.

17. Use of any of the following drugs or a plan to use these drugs during the study;
    - New or planned dose changes of systemic corticosteroids. Stable doses (≥4 weeks before Visit S1) and topical steroids allowed.
    - CETP inhibitors within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months prior to screening (Week -5, Visit S1)
    - Mipomersen (6 months prior to screening, Week -5, Visit S1)
    - Lomitapide (3 months prior to screening, Week -5, Visit S1)
    - Apheresis (3 months prior to screening, Week -5, Visit S1)
    - Simvastatin ≥40 mg/day (4 weeks prior to screening, Week -5, Visit S1)
    - Red yeast rice extract-containing products are not allowed (2 weeks prior to screening, Week -5, Visit S1)
18. Planned initiation of the following drugs during the clinical trial or changes prior to randomization (Day 1, Visit T1):
    - Hormone replacement (6 weeks prior to randomization)
    - Thyroid replacement (6 weeks prior to randomization)
    - Diabetes medications (4 weeks prior to randomization)
    - Obesity medication (44 weeks prior to randomization)
19. Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
20. Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
21. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
23. Pregnant, breastfeeding, or intending to become pregnant within 30 days after last dose of study drug.
24. Patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9 are excluded.

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 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. Description of IMP

Table 4: Investigational Medicinal Products

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

[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.

8.2. Concomitant Medications

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

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

8.2.1. Lipid-Regulating Medications and Supplements

Patients will be required to be on stable lipid-modifying therapy(s), including a maximally tolerated statin for at least 4 weeks prior to screening. Maximally tolerated statin includes statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must be documented. Use of fibrates must be stable at least 6 weeks prior to screening. Gemfibrozil, a fibrate, is prohibited as per co-administration instructions defined in the statin label. Stable lipid-modifying therapy(s) includes, but is not limited to, monotherapies or combination therapies containing the compounds below:

Statins

- Atorvastatin (Lipitor®, Sortis®)
- Fluvastatin (Lescol®)
- Lovastatin (Mevacor®, Altoprev™)
- Pravastatin (Pravachol®)
- Pitavastatin (Livalo®, Lipostat®)
- Rosuvastatin (Crestor®)
- Simvastatin (Zocor®) (doses ≥40 mg/day are exclusionary)

Selective cholesterol and/or bile acid absorption inhibitors

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

Fibrates

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

PCSK9 inhibitors

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

Other

- Ezetimibe/simvastatin where simvastatin is less than 40 mg/day (Vytorin® 10/10 and 10/20 Inegy® 10 mg/20 mg are allowed)
- Atorvastatin/ezetimibe (Atozet®)

8.2.2. Prohibited Medications

Patients will not have used medications (monotherapies or combination therapies) listed below within the allotted time period prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks). Short-term intermittent use (<14 days) of pulse steroids are allowed. Topical steroids are allowed.
- Gemfibrozil (Lopid®) (as per co-administration instructions defined in the statin label) ≥6 weeks prior to screening (Visit S1)

- Cholestin (red yeast rice extract, also known as monascus purpureus extract) (≥2 weeks prior to screening)
- CETP inhibitors within the last 2 years prior to screening (Visit S1) except for evaceptrapib within the last 3 months prior to screening (Visit S1)
- Mipomersen within 6 months prior to screening (Visit S1)
- Lomitapide within 3 months prior to screening (Visit S1)
- Apheresis within 3 months prior to screening (Visit S1)
- Simvastatin ≥40 mg/day
- Ezetimibe/simvastatin where simvastatin doses are ≥40 mg/day (Vytorin® 10/40 and 10/80 and Inegy® 10 mg/40 mg and 10 mg/80 mg are exclusionary)

8.2.3. Allowable Medications

Other concomitant medications must be stable, 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

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

- Diabetes medications
- Antiobesity medications

8.3. Treatment Compliance

Screening Compliance

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

Placebo Run-in and Treatment Period Adherence

At Week -1 (S3) visit in the placebo run-in period and at each of the subsequent patient visits, designated clinical site staff will assess patient for placebo and/or 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. 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. However, patients with ≤80% adherence over the entire Run-in Period and/or who experienced a study drug-related AE, will not go onto randomization.

8.4. Blinding

Patients who satisfy all entry criteria during the screening and complete single-blind placebo run-in period and meet the lipid, safety, tolerability, and drug adherence measures will be randomized to a treatment group at Week 0 (Visit T1). Patients on maximally tolerated lipid-modifying therapy, as determined by the investigator, will be stratified based on the patient's CV risk (ASCVD alone; HeFH with or without ASCVD) and baseline statin intensity (high intensity statin, moderate intensity statin, low intensity statin) for a total of 6 strata. The Investigator or designee will contact IWRS at this visit to randomize the patient into the study. The IWRS will determine the randomized treatment assignment based on their HeFH status and baseline statin use and dose and assign a randomization number and the appropriate study drug container via medication identification numbers (MED ID).

After patients have been randomized, study drug, which is 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, including any plasma concentration of bempedoic acid and its metabolite that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, and CRO.

An independent blinded expert CEC will adjudicate all clinical endpoints, including death, using standardized definitions. Clinical endpoints will also be reported as SAEs. Additional details and definitions will be provided in a CEC Charter.

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 will be monitored by the DMC during this period. At each DMC review, relevant unblinded safety and efficacy information from ongoing studies will be provided to the DMC by an independent, unblinded ICON programmer and statistician. Additional details will be provided in a DMC Charter.

8.5. Overdose

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

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 [redacted] tablets) and matching placebo ([redacted] tablets). IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study.

The 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 100-day supply increments to patients by appropriate clinical site personnel. Patients will receive one 100-day supply bottle at Week 0 (Visit T1), Week 12 (Visit T4), and two 100-day supply bottles at Week 24 (Visit T5). At Week 12, patients will return their first bottle and tablets will be counted by study personnel who will then dispense a second bottle. At Week 24, tablets from the second bottle will be counted and the final 2 bottles dispensed. At Week 52, tablets will be counted by study personnel from the 2 bottles dispensed at Week 24.

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

9.2. Administration of Investigational Medicinal Product

Patients will be instructed to ingest, 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. IMP may be taken with or without food. On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed. If a patient arrives at clinic on Visits T4 or T5 or T7 without having fasted or having taken IMP before arriving at the clinic, reschedule the visit (the next day or as soon as possible) so that the fasting and dosing requirements have been met. Patients will be instructed to return all packaging and unused IMP at each clinic visit.

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

9.3. Investigational Medicinal Product Accountability

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

IMP 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 for all IMP
- Dates and initials of person(s) responsible for IMP inventory (including entry/movement/disposition)
- Date and amount of IMP dispensed to each patient, including unique patient identifiers
- Date that IMP 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 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 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 ± 7 days)

The screening period will begin with a screening visit that will occur approximately 5 weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history, including assessment of HeFH status and ASCVD
- Concomitant and prohibited medication review
- Height (cm), weight (kg), BMI
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, coagulation, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - HbA_{1C}
  - TSH
  - FSH (in appropriate female patients)
  - Serum pregnancy test (on appropriate female patients)
- Serology (including HBsAg, HCV)

- Review of all inclusion/exclusion criteria that can be assessed at this time
- 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 therapy(s) 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).

Note:

- An optional visit approximately 1 week later MAY be completed if patient fails TG entry criterion. If this optional visit is completed, the repeat lipid values will be used to determine eligibility.
- An optional visit between Visits S1 and S2 may be scheduled to collect screening fasting labs in the event that the patient arrives at Visit S1 in a nonfasted state.
- An optional visit between Visits S1 and S2 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after BP medications have been adjusted, they have been on stable doses of BP medications for at least 2 weeks, and the repeat BP values (DBP and/or SBP) no longer meet exclusionary values.
- An optional visit between Visits S1 and S2 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated 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.

10.2.2. Placebo Run-in Week -4 (Visit S2; Day -28± 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

The patient will undergo the following assessments and procedures at (Visit S2)

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

- Conduct diet and exercise counseling
- IWRS contact to obtain the and MED ID number for single-blind placebo
- Dispense placebo and provide dosing instructions (one 35-day supply bottle)
- Schedule next visit

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

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints (starting from signing of the informed consent document)
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG); LDL-C must be ≥70 mg/dL (1.8 mmol/L) to be eligible
- Conduct diet and exercise counseling
- Re-dispense placebo container from Visit S2 to patient for continued dosing and provide dosing instruction
- Assessment and recording of drug compliance
- 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 the 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.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Physical examination (PE)
- Weight
- 12-Lead electrocardiogram (ECG)

- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis

    Note: Urine pregnancy test (for females of childbearing potential)
  - Coagulation in patients on vitamin K antagonists only (and repeat 3-5 days later)
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- Review inclusion/exclusion criteria to establish patient eligibility
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions (one 100-day supply bottle)
- Return of placebo tablets, record compliance and ensure patient meets eligibility criteria
- Schedule next visit

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

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.3.2 for the list of the required assessments. The patient will be asked to continue to be followed for safety 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 52 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 Week 4 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)
- Weight
- Vital signs

- Clinical 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
- Return of IMP; assessment and recording of IMP compliance
- Re-dispense IMP container from Visit T1 to patient for continued dosing and provide dosing instruction
- Schedule next visit

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

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

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Diet and exercise counseling
- Assessment of study drug dosing adherence

Note: If the patient discontinues at or between study visits, please proceed to Section 10.3.2 for detailed instructions.

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

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.10 for the list of the required assessments. The patient will be asked to continue to be followed for safety using the protocol-specified visit schedule. If the patient consents for follow-up, schedule the next protocol-specified visit.

Patients who do not provide consent 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 52 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 Week 12 (Visit T4):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)
- Weight
- Vital signs

- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP and provide dosing instructions (one 100-day supply bottle)
- Schedule next visit

10.2.8. Treatment Week 24 (Visit T5; 168 ±7 days)

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.10 for the list of the required assessments. The patient will be asked to continue to be followed for safety using the protocol-specified visit schedule. If the patient consents for follow-up, schedule the next protocol-specified visit.

Patients who do not provide consent 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 52 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 Week 24 (Visit T5):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}

  - hs-CRP
- PK sample before dose
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP and provide dosing instructions (two 100 day supply bottles)
- Schedule next visit

10.2.9. Treatment Week 36 / Telephone Visit (Visit T6; 252 ±3 days)

Patients will undergo the following assessments via telephone at Week 36 (Visit T6):

- Concomitant medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints
- Diet and exercise counseling
- Assessment of study drug dosing adherence

Note: If the patient discontinues at or between study visits, please proceed to Section 10.3.2 for detailed instructions.

10.2.10. Treatment Week 52/EOS (Visit T7; 365 ±7days)

Patients will undergo the following assessments and procedures at Week 52 (Visit T7), when completing an End of Study (EOS) visit, withdrawing from study (early withdrawal), or withdrawing from IMP treatment:

Patients will undergo the following assessments and procedures at Week 52 (Visit T7):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)
- PE
- Weight
- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - apoB
  - HbA_{1C}

  - hs-CRP
  - PK sample before dose
- Return of IMP; assessment and recording of IMP 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 52 (Visit T7) to be considered as having completed participation in the study.

Patients who withdraw from IMP prior to Week 52 (Visit T7) 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 prior to Week 52 (Visit T7) 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 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 52 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.

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, all End of Study procedures should be completed. Reason for withdrawal, date of the discontinuation, and date of the last dose of study drug should be recorded in the appropriate section of the eCRF. Additionally, the discontinuation visit date must be registered in IWRS. Study drug assigned to the withdrawn patient may not be assigned to another patient.

All effort should be made to have each patient complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed. Except in the case of a medical emergency, the procedures and assessments detailed in Section 10.2.10 will be performed upon the discontinuation of the study.

Patients choosing to withdraw from the study early should be encouraged to return for all study scheduled clinic visit even if they are no longer taking IMP. Patients who withdraw from all aspects of the study will be asked to consent to clinical visits or phone calls for safety assessments, including AEs, concomitant medication, and current health status through Week 52 (Visit T7).

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 DBP and SBP as well as heart rate.

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

11.1.3. Weight, Height, and Body Mass Index

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

Height will be measured using standard clinic procedures.

BMI will be calculated using the formula:

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

11.1.4. Physical Examination

PEs will include an assessment of the following:

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

Documentation of the PE findings will be included in the source documentation at the clinical site. Significant findings 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 11.2.3.

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, and followed and evaluated with additional tests (if necessary) until the underlying cause is determined or the event is brought to an acceptable resolution. Additional clinical and laboratory information will be collected and carefully documented in order to better characterize the ECG abnormality and rule out alternative causes. ECG findings determined to be a clinically significant change from baseline should be reported as an AE regardless of causality.

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

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 5. Collection schedule, schedule of laboratory parameters by visit, and instructions are in the Clinical Laboratory Manual provided by Central Laboratory.

Table 5: Clinical Laboratory Parameters (Safety)

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

Table 5: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Coagulation (screening for all patients, T1 and 3-5 days after T1 in patients receiving anticoagulation therapy, only) • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • 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)	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • PK sample

[a] If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained.
[b] If 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. For collection and processing of PK samples, please see Section 11.1.6.5 and Section 11.1.6.6. Samples will be processed by the Central Laboratory.

Blood draws for lipids, TG, and glucose must meet the criteria listed below. If these criteria have not been met, these blood samples will NOT be collected. If these criteria 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 Investigator's responsibility to review the results of all laboratory tests as they become available and to sign and date the report to document their review. For each laboratory test outside of the laboratory normal range, the Investigator needs to ascertain if this is a clinically

significant change from baseline for the individual patient, with baseline defined as the last value or observation before the first dose of study drug. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the patient, the Investigator should determine if it qualifies as an AE, and if yes, an appropriate eCRF will be completed.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause or resolution. Specific monitoring and management guidelines for laboratories of special interest are outlined in the sections below.

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 × 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), HCV (confirmation of screening measurement), and anti-cytomegalovirus/immunoglobulin M; 2) history of concomitant medication use; 3) history of exposure to environmental chemical agents, including ethanol; and 4) query for related symptoms. Additionally, further testing such as liver ultrasound or magnetic resonance imaging (MRI) scanning may be warranted to rule out additional pathology depending on clinical presentation and should be discussed with the Sponsor personnel or the authorized Medical Monitor.

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN, consideration should be given to withdrawing the patient and administering no further doses of study drug. At the investigator's discretion, study drug may be interrupted and the patient rechallenged with study drug after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >5 × ULN, patient should be withdrawn from 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 if deemed by the investigator.
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further 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 if deemed by the investigator:

- TB >2 × ULN

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

- INR >1.5 × ULN (unless the patient is on stable dose of anticoagulation medication)
- Appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia

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 m^2) or if the patient experiences acute renal failure, the patient should be withdrawn from IMP treatment but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1)

11.1.6.3.3. Monitoring and Management of Hemoglobin Change

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

Repeat hematology assessment will include: 1) measurement of Hgb, hematocrit (Hct), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, reticulocyte count (percent and absolute), red blood cell count (RBC), and white blood cell count (WBC) with differential (absolute values only); 2) history of concomitant medication use; and 3) query for related symptoms. Additionally, further testing may be warranted to rule out additional pathology depending on clinical presentation, and should be discussed with Esperion Therapeutics personnel or the authorized Medical Monitor.

- If repeat Hgb assessment confirms a decrease >2.0 g/dL (20 g/L) from baseline, the patient should be monitored carefully during the study and return at 2-week intervals after study completion for additional Hgb measurement until the level returns to baseline or reaches a stable level.
- If repeat Hgb assessment confirms Hgb <8 g/dL (80 g/L), the patient should be withdrawn from 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 × ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat CK assessment will include query for related symptoms.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic the patient should receive further assessment and investigation into the cause, assess whether there is renal injury and measure CK approximately weekly or more frequently if clinically indicated until resolution. If CK levels continue to rise; IMP should be discontinued.
- If symptomatic, the following should be completed:
  - Hold IMP
  - 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 × 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).

11.1.6.4. 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 will occur. This event should be captured as an AE.

11.1.6.4.1. Monitoring and Management of Elevated LDL-C

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and ≥25% from the patient's baseline value at Week 0, (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
  - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
  - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at doses ≥40 mg/day and the fibrate, gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).
  - The initiation of any new or dose changes of any existing lipid-lowering treatment will be documented on the eCRF as a concomitant medication with the associated start date
  - Patients who have their lipid-lowering medications modified, including new medications or dosage changes to existing medications, should return to the clinic in 4 weeks after the modification to their lipid-lowering treatment for a routine

safety laboratory assessment. Additional safety laboratory assessments may be conducted at the investigator's discretion.

- Adjunctive therapy medications will not be provided by the sponsor
- Patients continuing to exceed the LDL-C threshold after maximizing the standard-of-care LCL-C-lowering therapy and, in the opinion of the investigator, require therapies that are prohibited by the protocol 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 11.7 for sample collection and instructions.

11.1.6.4.2. 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 (however, gemfibrozil may not be added) to lower TG using a patient-specific prescription. The initiation of this medication will be documented on the case report form as a concomitant medication with the associated start date. These medications will not be provided by the sponsor.
- Patients continuing to exceed the TG threshold after maximizing the standard-of-care triglyceride-lowering therapy will be discontinued from 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 11.7 for sample collection and instructions.

11.1.6.5. Pharmacokinetic Assessments

Pharmacokinetic assessments to measure plasma concentrations of bempedoic acid 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 bempedoic acid and ESP15228 will be conducted by the Bioanalytical Laboratory.

11.1.6.6. Collection and Assessment of Pharmacokinetic Samples

Pharmacokinetic samples will be collected from patients at Weeks 24 and 52, for use in further developing the population PK model.

Plasma concentrations of bempedoic acid 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.

11.1.6.7. Shipment of Pharmacokinetic Samples

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

11.1.6.8. 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 to the Investigator through 30 days following the last dose of study drug. Beginning with Visit S1 (Week -5), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. Any SAE that occurs from the time of ICF through 30 days following the last dose of study drug should be reported to the Sponsor per Section 11.3.

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

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

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

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

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

- Investigator's assessment of relationship to study drug.

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

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

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

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 between the study drug and the AE. The degree of "relatedness" of the AE to the study drug may be described using the following scale:

- Not Related: No temporal association and other etiologies are likely the cause
- Unlikely: While cannot be definitively ruled as not related to IMP, a causal association is remote, and other etiologies are more likely to be the cause. For reporting and summarization, events assessed as "Unlikely" to be related to IMP will be considered as "Not Related" to IMP for regulatory reporting purposes.
- Possible: Temporal association, but other etiologies are likely the cause. However, involvement of the study drug cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the study drug is discontinued.

- Definite: Established temporal association with administration of the study drug with no other more probable cause. Typically, the event should resolve when the study drug is discontinued and recur on re-challenge.

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. Admission to the hospital for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

11.2.7.2. Events not Qualifying as Serious Adverse Events

The following is not considered an SAE and therefore does not need to be reported as such:

- 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 central (or local where appropriate) laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. For criteria of reporting abnormal lab values as AE, see Section 11.1.6.3.

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, must be reported by the Principal Investigator or designee to the authorized Medical and Safety Services within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. For most patients this will be 30 days following their Week 52 (Visit T7) visit. All SAEs that the Investigator considers related to study drug that occur after the 30-day follow-up of the study period must be reported to the Sponsor.

To report the SAE, complete the SAE information in the clinical electronic data capture (EDC) database within 24 hours of becoming aware of the occurrence. Additional information, such as diagnostic test results or hospital discharge summary can be sent via email [redacted] or via fax ([redacted]).

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

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

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

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the safety contact information provided on the SAE report form.

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

If a female patient becomes pregnant during the study or within 30 days after the last dose of study drug, the investigator is to stop dosing with study drug(s) immediately. A pregnancy is not considered to be an AE or an SAE; however, it must be reported to the Sponsor / SAE designee using the paper Pregnancy Report Form within the same timelines as an SAE. A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the paper Pregnancy Outcome Report Form should be completed and reported to the Sponsor. Adverse events or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE CRF. Patients who become pregnant will discontinue IMP immediately and complete the End of Study evaluations.

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 ETC-1002, uric acid and hemoglobin will be closely monitored. Safety monitoring guidelines for hemoglobin is 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 primary hyperlipidemia and mixed dyslipidemia 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. AESI monitoring will also include the following:

- AEs associated with the experiences with bempedoic acid to date:

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

  In general, laboratory results showed no clinically significant trends at the data cut-off for End-of Phase 2. A total of 7 patients receiving bempedoic acid monotherapy or in combination with a statin or ezetimibe experienced repeated and confirmed ALT and/or AST >3 × the ULN; in 1 of these patients receiving bempedoic acid 80 mg the elevation was assessed by Investigator as not related to study drug because the patient tested positive for acute cytomegalovirus (CMV) infection. One patient receiving ezetimibe monotherapy experienced repeated and confirmed ALT and/or AST >3 × ULN. All LFT abnormalities were considered mild to moderate and improved upon removal of the study drug. Clinical chemistries, hematology, vitals, physical examinations, and ECGs will be routinely monitored in the bempedoic acid clinical program.

- Potential AEs based on findings in nonclinical models:

  Hypoglycemia and metabolic acidosis led to monkey deaths in preclinical studies. Exposures in these studies were >17 times higher than those associated with the bempedoic acid 180-mg dose which will be evaluated in this study. Subsequent monkey studies proved that hypoglycemia was reversible with discontinuation of study drug and nutritional support. No cases of either hypoglycemia or metabolic acidosis have been identified in Phase 1 or 2 clinical trials to date. Patients in all

clinical trials will be provided with information (in the ICF) regarding the signs and symptoms of hypoglycemia including lightheadedness, shakiness, shaking of the hands, sweating, tingling, blurred visions, nausea or vomiting, mental confusion, difficulty concentrating and drowsiness. Patients who experience any of these symptoms will be instructed to report them to their study doctor. Diabetes/glycemic monitoring plans are Section 11.1.6.4. Occurrence of metabolic acidosis will be monitored by clinical safety laboratory chemistries.

- AEs that are currently monitored for all experimental lipid-lowering therapies and have been associated with previous lipid-lowering therapies:

  Hepatic: Hepatic function will be monitored throughout with the clinical safety labs. More detailed investigation will occur if the safety clinical laboratory results are 3 times or more than the ULN (see Section 11.1.6.3.1).

  Muscle: Muscle events have been associated with statins (Thompson 2003) and other lipid-lowering therapies and are mentioned in the product information for those products. The exact mechanism in the development of muscle events is unclear. Bempedoic acid is a prodrug which needs to be converted by an acyl-CoA synthetase (ACS) to a coenzyme A (CoA) ester (ETC-1002-CoA). The specific ACS known to convert bempedoic acid into its active form is not present in skeletal muscle. This suggests that bempedoic acid may not lead to an increase in muscular side effects when given in conjunction with statins. Nonetheless, muscle symptoms through AE review, CK elevations, and symptoms of potential myopathy will be closely monitored. More detailed investigation will occur if results exceed 5 x ULN (see Section 11.1.6.3.2).

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

  Renal: Nonclinical studies have demonstrated nephrotoxic effects on tubular cells of some lipid-modifying agents. In the Phase 2 program, creatinine elevations >25% over baseline occurred in 1 subject in the bempedoic acid 80 mg, 2 in the 180 mg, 1 in the 180 mg + ezetimibe, 1 in the 240 mg, and 3 in the 240 mg + baseline statin. In most cases, this elevation occurred at the end of the study and the values were not repeated and the events were not considered related. In 1 case, repeat values were obtained and the subject's creatinine was returning to baseline by Week 12. None exceeded a serum creatinine >1.8 mg/dL. No subjects withdrew due an AE of increased creatinine. In the Phase 3 program, repeat evaluation of creatinine will occur and patients exceeding protocol-specified values will be withdrawn from study medication (see Section 11.1.6.3.2). Patients will be monitored beyond the

conclusion of the study if necessary to follow abnormal renal laboratory values until resolution or stabilization.

Cardiovascular Events: The occurrence of clinical endpoints will be monitored and adjudicated by an independent blinded CEC throughout the bempedoic acid program. The details of the monitoring program can be found in the charter of the CEC. Standard monitoring will include occurrence of CV AEs, SAEs, both as adjudicated by the CEC, standard vital signs, and ECGs.

Neurocognitive Events: Theoretically, it is possible that lipid-lowering agents that disrupt cholesterol homeostasis in the brain could impact neurological function, and there have been reports of cognitive impairment (eg, memory loss) associated with the use of statin drugs (FDA 2012). The human brain has a significant requirement for cholesterol (Dietschy 2001; Dietschy 2004) and dysregulation of brain cholesterol homeostasis has been linked to chronic neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, Niemann–Pick type C disease and Smith-Lemli-Opitz syndrome (Goedeke 2014). In the Phase 2 program, the only disorder in this system organ class (SOC) that occurred more commonly in the bempedoic acid treated group was headache. For the ongoing program, neurocognitive events will be evaluated by standard PE and adverse monitoring. Summarization of events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms.

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 (CEC)

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

11.7. Assessment of Lipid Endpoints

11.7.1. Lipid Parameters

After randomization, patients will return to clinic every 4 weeks for the first 12 weeks, then again 12 weeks later at Week 24 (Visit T5) and at Week 52 (Visit T7). Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, HDL-C, TC, apoB, and TG at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

11.7.2. Clinical Laboratory Tests (Lipids)

Clinical laboratory samples will be collected at all clinic visits.

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 6. 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 6: Clinical Laboratory Parameters (Lipids) and Cardiometabolic Biomarkers

Clinical Laboratory Test	Clinical Laboratory Test
Basic Lipid Parameters • Total cholesterol (TC) • low-density lipoprotein cholesterol (LDL-C) and non-HDL-C • High-density lipoprotein cholesterol (HDL-C) • Triglycerides (TG)	Other Parameters • 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 2 documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

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 500 randomized patients in the bempedoic acid 180 mg group and 250 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 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 ($\alpha = 0.05$) and a common standard deviation of 15%. The sample size of 500 randomized patients in the bempedoic acid 180 mg group and 250 randomized patients in the placebo group gives a total study sample size of 750.

12.3. Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy summaries and 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 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 Endpoint

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a

covariate. Baseline LDL-C is defined as the mean of the LDL-C values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the LDL-C values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). If only one value is available, then that single value will be used for baseline. 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 group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a covariate. Approximately 200 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. 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. Details for PMM and multiple imputation will be descried in the SAP.

12.6. Secondary and Tertiary Efficacy Endpoints

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

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

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

In general, change or percent change in lipid parameters at a given time point will be analyzed using similar ANCOVA model for the primary endpoint with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and the relevant baseline as a covariate.

Baseline for HDL-C, non-HDL-C, TG, and TC will be defined as the mean of the lipid values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the lipid values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP will be defined as the predose Day 1/Week 0 (Visit T1) value.

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

The ANCOVA assumption of normality will be assessed. If 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.

Percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed similarly with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI, and p-value.

12.7. Additional Post-randomization Adjunctive LDL-lowering or Triglyceride-Modifying Therapy

The number and percent of patients in each treatment group requiring additional (post-randomization) adjunctive LDL-C or triglyceride-modifying therapy will be summarized. Medications and the reasons for their additional treatment (hyperlipidemia vs. hypertriglyceridemia) will be summarized separately.

12.8. Safety Endpoints

The summarization of AEs will include 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, coagulation, HbA_{1C}, glucose, and urinalysis; PE findings; vital signs; ECG readings; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each postbaseline time point.

Hepatic Safety

Liver-associated enzymes and TB will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST, and TB. Hy's law criteria (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN or patient's baseline) will also be applied to the data; any potential Hy's law cases will be listed separately. In the case of patients with Gilbert's disease, TB will be fractionated and the determination of 2 × ULN based upon direct (conjugated) bilirubin. For patients with Gilbert's Disease 2 × the conjugated bilirubin will be used as the criterion.

Musculoskeletal Safety

AEs of muscle-related symptoms will be summarized by treatment group. CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal CK values will be summarized. These summaries of patients with abnormal CK will be performed overall; by normal baseline CK; and by abnormal baseline CK.

Diabetes and Hyperglycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group. Glucose and HbA_{1C} will be monitored at baseline and at Weeks 12, 24, and 52, and be summarized.

Renal Safety

Baseline eGFR will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using prespecified MedDRA terms and will be performed by SOC, severity, and relationship to study drug for each 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.

12.9. Pharmacokinetics

Trough plasma concentrations of bempedoic acid and ESP15228 will be collected and summarized from patients prior to dose at Weeks 24 and 52 for use in further developing the population PK model.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation (ICH) and 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.

13.2. Audits and Inspections

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

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

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

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 13.2 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 the Study

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

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

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

The Investigator will assure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperates with monitoring and audits, and will demonstrate due diligence in recruiting and screening study patients. The Investigator must sign and return to the Sponsor the "Investigator's Signature" page (see Appendix 3) and provide a copy of current curriculum vitae. For this study and all studies conducted under an IND, 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.

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

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

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.

17. ADMINISTRATIVE CONSIDERATIONS

17.1. Investigators

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

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

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

17.2. Study Administrative Structure

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

Bioanalytical Laboratory:

Central Laboratory:

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

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.

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

20. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

	Screen	Run-in		Treatment						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5**	**T6/phone**	**T7/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**
Procedure	**Day --35± 7**	**Day -28± 3**	**Day -7± 3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 168±7**	**Day 252±7**	**Day 365 ±7**
Informed Consent	X									
Enrollment Criteria	X									
Demographics	X									
Medical History	X									
HeFH Status Determination	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X
Physical Exam				X						X
Weight[4]	X			X	X		X	X		X
Height/BMI	X									
12-Lead ECG[5]				X						X
Vital Signs[6]	X	X	X	X	X		X	X		X
Serology[7]	X									
Serum Pregnancy and/or FSH[8]	X									
Urine Pregnancy Test[8]				X						
TSH	X									
Clinical Safety Labs[9]	X			X	X		X	X		X
Basic Fasting Lipids[10]	X		X	X	X		X	X		X
HbA_{1C}	X			X			X	X		X
apoB				X			X	X		X
hs-CRP				X			X	X		X
Diet and exercise counseling[11]	X	X	X	X	X	X	X	X	X	X
Plasma PK								X		X
Establish Patient Eligibility				X						
Randomization				X						
IWRS Contact	X	X		X			X	X		X[12]
Single-Blind Drug Dispensing		X								
Double-blind Drug Dispensing[13]				X			X	X		
Drug Return/Compliance			X	X	X		X	X		X
Schedule next visit	X	X	X	X	X	X	X	X	X	

NOTE: For patients who withdraw from IMP treatment, they will continue to have visits according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but refuse to come to the clinic for assessments, assessments will take place by phone. The telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death).

[1] An optional visit between Visits S1 and S2 may be completed if patient fails to meet TG entry criterion. If this optional basic fasting (minimum of 10 hours) lipid value visit is completed, the repeat lipid value will be used to determine eligibility.

[2] An optional visit between Visits S1 and S2 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and S2 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

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

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

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

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

[7] Serology for HBsAg, HCV

[8] Serum pregnancy test completed in premenopausal women only. FSH test is completed in women <55 years old and >1 year without menses. Urine pregnancy test in women of childbearing potential just prior to randomization.

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1) for all patients, Baseline (Visit T1) and 3-5 days after Visit T1 only if on anticoagulants). Please refer to laboratory manual for detailed schedule of tests. A local laboratory may be used for assessment at 3-5 days after Visit T1.

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

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

[12] IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

[13] Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS.

[14] If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

APPENDIX 2. SPONSOR'S SIGNATURE

Study Title: A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-047

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

Signed: [redacted]

Date: 10-May 2017

Study Title: A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-047

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

Signed: [redacted] Date: 09 May 2017

Study Title: A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-047

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

Signed: [redacted] Date: _____

[redacted]

Study Title: A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-047

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

Signed: [redacted] Date: 5-9-17

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title: A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy

Study Number: 1002-047

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. DUTCH LIPID CLINIC NETWORK CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

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

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

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

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

Scoring:

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

References:

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

APPENDIX 5. SIMON BROOME REGISTER DIAGNOSTIC CRITERIA FOR HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia[1]

Definite Familial Hypercholesterolemia:

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

  OR

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

Possible Familial Hypercholesterolemia:

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

  OR

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

References:

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

APPENDIX 6. SUMMARY OF CHANGES AMENDMENT 1

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-047
Study Title:	A Long-term Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy
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.
- Under Inclusion Criteria, revised the definition of true abstinence to reflect guidance from the Heads of Medicines Agency.
- Removed date within the body of the text on all pages within Appendix 2 as the date is included in the header
- Changed names and titles of Sponsor representatives providing signage on the protocol amendment

CHANGE 1 REVISION OF SPONSOR CONTACT AND PROTOCOL VERSION INFORMATION

Location:

Title Page; Sponsor Contact and Version

Original Text:

Sponsor Contact: [redacted]

New text:

Sponsor Contact: [redacted]

Original Text:

	Version	Date
	Original Protocol:	22 September 2016

New Text:

	Version	Date
	Amendment 1:	***18 January 2017***

CHANGE 2 REVISION OF INCLUSION CRITERIA

Location:

Synopsis, Diagnosis and criteria for patient eligibility, Inclusion Criteria, and Section 7.1, Subject Inclusion Criteria

Original Text:

4. Women must be either:
    - Naturally postmenopausal (as reported by the patient, defined as greater than 55 years and ≥1 year without menses, <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L), or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
    - Women of childbearing potential must be willing to use 1 acceptable method of birth control. The minimal requirement for adequate contraception it is that it 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 birth control medications; placement of an intrauterine device (IUD) 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; or true abstinence (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal).

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

New Text:

4. Women must be either:

   - Naturally postmenopausal (as reported by the patient, defined as greater than 55 years and ≥1 year without menses, <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L), or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential must be willing to use 1 acceptable method of birth control. 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 birth control medications; placement of an intrauterine device (IUD) 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; or true abstinence ***when this is in line with the preferred and usual lifestyle of the subject*** (~~not including~~ periodic abstinence ***[eg,*** ~~such as~~ calendar, ovulation, symptothermal, postovulation methods~~, or *withdrawal*~~***], declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception).***

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

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: _____

[redacted]

New text:

Signed: _____ Date: _____

[redacted]

Original text:

Signed: _____ Date: _____

[redacted]

New text:

Signed: _____ Date: _____

[redacted]

APPENDIX 7. SUMMARY OF CHANGES AMENDMENT 2

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-047
Study Title:	A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy
Protocol Version Incorporating Current Summary of Changes:	Amendment 2: 22 March 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.
- Updated text pertaining to bempedoic acid mechanism of action based on new information.
- Reduced planned patient enrollment from 750 to 525 with 350 randomized to bempedoic acid 180 mg and 175 randomized to matching placebo. Reducing sample size has no impact on the statistical power with respect to the efficacy endpoints as this study was originally over-sized to provide a higher number for the exposure dataset. The sample size of 350 randomized patients in the bempedoic acid 180 mg group and 175 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 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 ($\alpha = 0.05$) and a common standard deviation of 15%. Text and figures where patient numbers are presented were updated accordingly.

- Removed the requirement that strata (statin dose and patient status) could not be capped in order to ensure adequate numbers of patient characteristics if imbalance occurs.
- Revised secondary and tertiary endpoints as well as added safety endpoints to more accurately describe statistical testing and analysis.
- Added additional clinical and telephone visits for patients taking simvastatin 40 mg based on a request from the Food and Drug Administration (FDA).
- Added implantable, injectable, or topical method as allowable forms of hormonal contraception.
- Added requirement that women use 2 rather than 1 form of acceptable contraception based on a request from the European Heads of Medicines Agency's Voluntary Harmonization Procedure review of another Esperion sponsored protocol. This amendment is to maintain consistency across protocols and is not based on any new data with bempedoic acid.
- Added additional fasting LDL-C assessment (Week -1 (Visit S3) ≥70 mg/dL (1.8 mmol/L) after the Run-in period to inclusion criteria. Removed the allowance of repeating a screening LDL-C measurement after Visit S1.
- Clarified the timing of the collection of lipid values with reference to PCSK9 inhibitor injections in order to ensure lipid values are obtained at trough levels of PCSK9.
- Further defined inclusion criteria around peripheral arterial disease and cerebrovascular atherosclerotic disease.
- Based on a request from the FDA, added eGFR <45 mL/min/1.73m^2 in patients taking simvastatin as exclusionary.
- Based on the extremely long half-live of experimental siRNA inhibitor, Inclisiran, excluded patients who have enrolled in a study of an experimental siRNA inhibitor of PCSK9.
- Clarified time period during which subjects should not intend to become pregnant.
- Altered the 3-month time period for not using the following drugs prior to screening based on the half-life of these medications: expanded mipomersen to 6 months and reduced simvastatin to 4 weeks as well as reduced the time period for use of obesity medications from 3 months to 4 weeks prior to randomization.
- Removed collection of optional genetic sampling.
- Removed collection of reserve samples.

- Removed collection of pharmacokinetic (PK) sample collection on Day 1 and clarified that collection needs to be prior to dosing at visits where PK samples are collected.
- Added windows (eg, ± 3 or ± 7 days) to all visits.
- Removed manufacturing contact details from the protocol and indicated the details will be described in the pharmacy manual.
- Based on a request from the FDA, the monitoring and management of CK values for asymptomatic patients was modified.
- Revised statistical sections to clarify level of significance, standard deviation, and methods for imputation of missing data.
- Added details to clarify the time period and reporting process for collection of AEs throughout the protocol as required.
- Added the following sections to the protocol:
  - **Definition of Serious Adverse Event Events or Outcomes not Qualifying as Serious Adverse Events**
  - **Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events**
- Made administrative changes throughout the protocol where required to correct inconsistencies, add clarification, or correct errors.

CHANGE 1 REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page

Original Text:

	Version	Date
	Amendment 1:	18 January 2017

New Text:

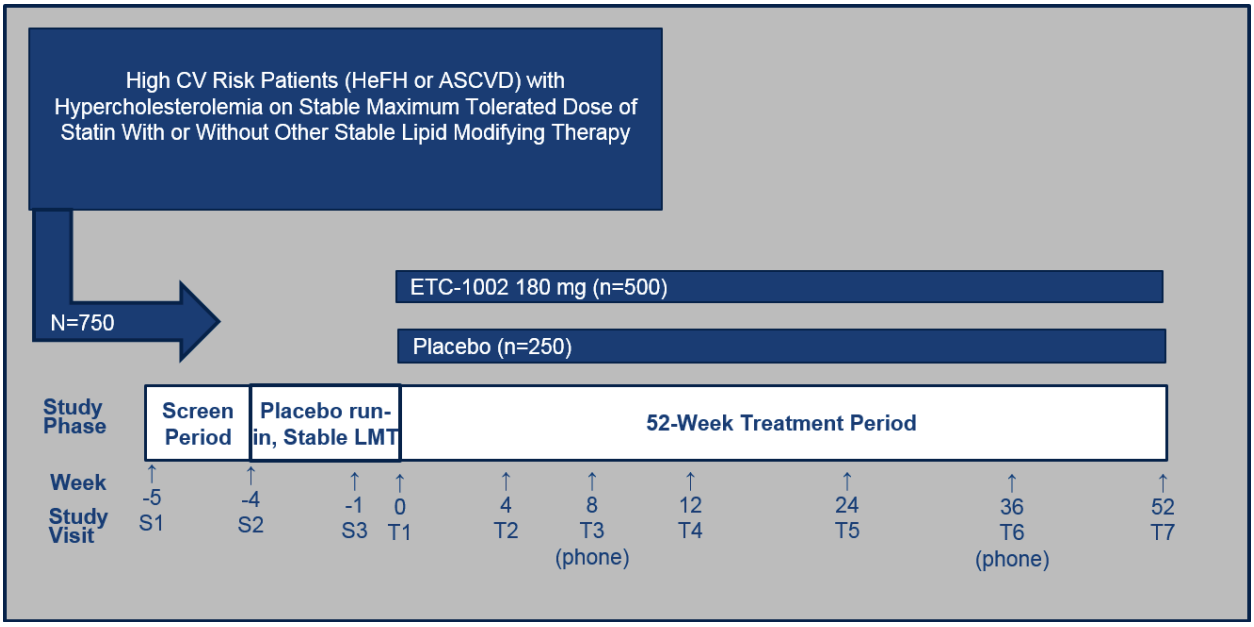
	Version	Date
	Amendment 1:	18 January 2017
	Amendment 2:	***22 March 2017***

CHANGE 2 STUDY DESIGN FIGURE REVISIONS

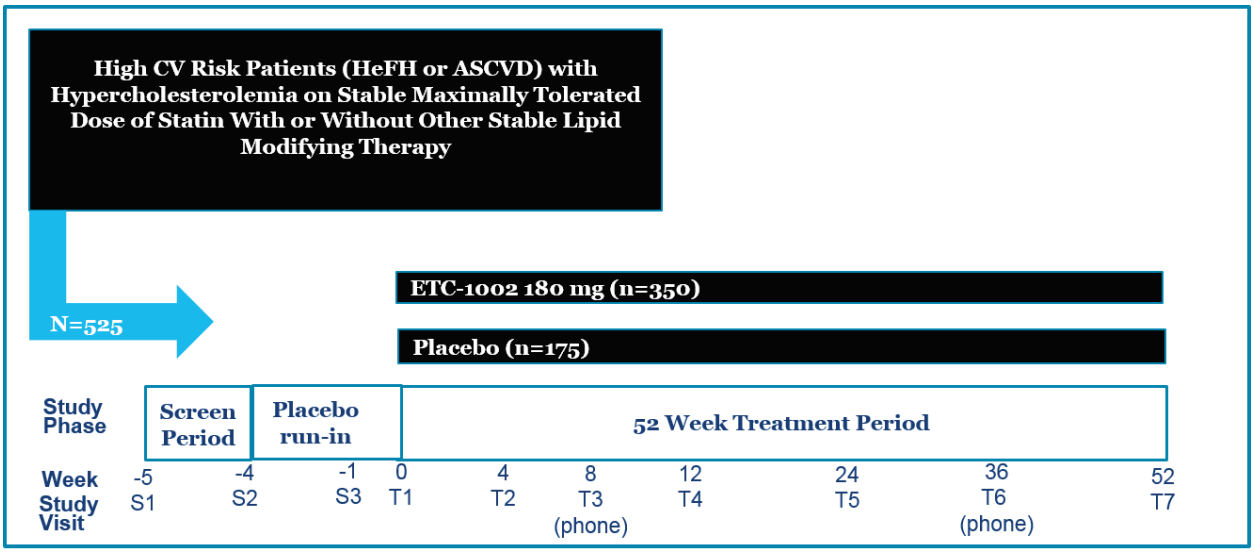
Location:

Section 2, Synopsis; 6.1 Overall Study Design

Original Text:



New Text:



CHANGE 3 EFFICACY AND SAFETY ENDPOINT REVISIONS

Location:

Section 2, Synopsis; Section 5.2.2, Secondary Endpoints; Section 5.2.3, Tertiary Endpoints

Original Text:

5.2.2 Secondary Endpoints

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

5.2.3 Tertiary Endpoints

Tertiary efficacy endpoints are of interest:

1. Change and percent change from baseline to Week 52 in LDL-C
2. Percent change from baseline to Weeks 24 and 52 in non-HDL-C, TC, apoB, and hs-CRP
3. Percent change from baseline to Weeks 12, 24, and 52, in TG and HDL-C

New Text:

5.2.2 Secondary Endpoints

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

5.2.3 Tertiary Endpoints

Tertiary efficacy endpoints are of interest:

1. ***Absolute c***~~C~~hange and percent change from baseline to Week 52 in LDL-C
2. Percent change from baseline to Weeks 24 and 52 in non-HDL-C, TC, apoB, and hs-CRP
3. Percent change from baseline to Weeks 12, 24, and 52, in TG and HDL-C

5.2.4 Safety Endpoints

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

CHANGE 4 SUBJECT INCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis; Section 7.1, Subject Inclusion Criteria

Original Text:

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. Men and nonpregnant, nonlactating women.
4. Women must be either:

   - Naturally postmenopausal (as reported by the patient, defined as greater than 55 years and ≥1 year without menses, <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L), or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential must be willing to use ~~1~~ ***2*** acceptable method***s*** of birth control. The minimal requirement for adequate contraception it is that it 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 birth control medications; placement of an intrauterine device (IUD) 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; or 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 the trial, and withdrawal are not acceptable methods of contraception).

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

5. Fasting LDL-C (minimum of 10 hours) value at Week -5 (Visit S1) ≥100 mg/dL (2.6 mmol/L)

   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.

6. Have high CV risk that is defined as either:

   - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established CHD or CHD risk equivalents.

     OR

   - Have ASCVD (with established CHD or CHD risk equivalents)

     Documented history of CHD (includes 1 or more of the following):

     – Acute MI

     – Silent MI

     – Unstable angina

     – Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)

     – Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

     Documented CHD risk equivalents (includes 1 or more of the following criteria):

     – Peripheral arterial disease

     – Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease

       Note: Patients with T2DM are allowed in this study; however, for this study T2DM is not considered a CHD risk equivalent

7. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin either alone or in combination with other lipid-lowering therapies, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed as per co-administration instructions defined in the statin label). Maximally tolerated statin includes statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must be documented.

A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

Note: Patients can be on any available lipid-modifying therapy with the exception of the exclusions listed below as long as they have been stable for 4 weeks prior to Screening Visit S1 and are taken at a consistent time each day. In the case of PCSK9 inhibitor use, the patient must have received 3 stable doses and all lipid values obtained 1-2 days prior to their next dose. Patients must have not discontinued investigational or commercial PCSK9 inhibitor within 4 months prior to Screening Visit S1.

New Text:

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. Men and nonpregnant, nonlactating women.
4. Women must be either:
   - Naturally postmenopausal (as reported by the patient, defined as greater than 55 years and ≥1 year without menses, <55 years and ≥1 year without menses with follicle-stimulating hormone (FSH) ≥40.0 IU/L), or surgically sterile including hysterectomy, bilateral oophorectomy, or tubal ligation or;
   - Women of childbearing potential must be willing to use ~~1~~ ***2*** acceptable method***s*** of birth control ***(unless they have agreed to follow the definition of true abstinence)***. The minimal requirement for adequate contraception it is that it 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 (IUD) 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; or 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 the trial, and withdrawal are not acceptable methods of contraception).

   There are no protocol-specific birth control requirements for men with partners who are able to become pregnant.
5. Fasting LDL-C (minimum of 10 hours) value at Week -5 (Visit S1) ≥100 mg/dL (2.6 mmol/L) ***and fasting LDL-C value at Week -1 (Visit S3) ≥70 mg/dL (1.8 mmol/L)***

   ~~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.~~

6. Have high CV risk that is defined as either:

   - Diagnosis of HeFH. Diagnosis must be made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that is >8 points (see Appendix 4) or the Simon Broome Register Diagnostic Criteria with an assessment of 'Definite HeFH' (see Appendix 5). Patients with a diagnosis of HeFH may or may not have established CHD or CHD risk equivalents.

     OR

   - Have ASCVD (with established CHD or CHD risk equivalents)

     Documented history of CHD (includes 1 or more of the following):

     – Acute MI

     – Silent MI

     – Unstable angina

     – Coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery)

     – Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

     Documented CHD risk equivalents (includes 1 or more of the following criteria):

     – ***Symptomatic*** peripheral arterial disease ***(PAD) defined as***

       ○ ***peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 performed by a vascular lab or***

       ○ ***angiogram (including computed tomographic angiography [CTA]) showing ≥50% stenosis or***

       ○ ***peripheral arterial revascularization (surgical or percutaneous) occurring greater than 90 days prior to Visit S1 or***

       ○ ***abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair occurring greater than 90 days prior to Visit S1 or***

       ○ ***lower extremity amputation due to peripheral vascular disease occurring greater than 90 days prior to Visit S1***

     – ***Cerebrovascular atherosclerotic disease defined by:***

       ○ ~~Previous i~~***I***schemic stroke ***occurring greater than 90 days prior to Visit S1 or***

       ○ ***Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram occurring greater than 90 days prior to Visit S1.*** ~~with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of~~

~~atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease~~

Note: Patients with T2DM are allowed in this study; however, for this study T2DM is not considered a CHD risk equivalent

7. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin either alone or in combination with other lipid-lowering therapies, at stable doses and regimens for at least 4 weeks prior to screening (6 weeks for fibrates; however, gemfibrozil is not allowed as per co-administration instructions defined in the statin label). Maximally tolerated statin includes statin regimens other than daily dosing, including no to very low doses, but reasons for not using high-intensity statin dosing must be documented.

   A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

   Note: Patients can be on any available lipid-modifying therapy with the exception of the exclusions listed below as long as they have been stable for 4 weeks prior to Screening Visit S1 and are taken at a consistent time each day. In the case of PCSK9 inhibitor use, the patient must have received 3 stable doses. ***It is important that lipid values are measured at PCSK9i trough levels. Therefore, study visits should be scheduled in accordance with the patient's PCSK9i injection regimen so that measurement of lipid values for all visits occurs before the PCSK9i injection but not greater than 48 hours before the next scheduled PCSK9i injection.*** ~~and all lipid values obtained 1-2 days prior to their next dose~~. ***Patients*** ~~*must have not*~~ ***who have discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least*** ~~*within*~~ ***4 months prior to Screening Visit S1.***

CHANGE 5 SUBJECT EXCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis; Section 7.2, Subject Exclusion Criteria

Original Text:

1. Total fasting (minimum of 10 hours) triglyceride ≥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.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73m^2 at Week -5 (Visit S1) (Levey 2006).

   Note: At the discretion of the investigator, the screening period may be extended up to 4 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility.

New Text:

1. Total fasting (minimum of 10 hours) triglyceride ≥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~~ ***between Visits S1 and S2.*** For those patients who have a repeat TG, the repeat value will be used to determine eligibility.

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73m^2 at Week -5 (Visit S1) (Levey 2006). ***In patients taking simvastatin 40 mg, eGFR <45 mL/min/1.73 m^2 is exclusionary.***

   Note: At the discretion of the investigator, the screening period may be extended up to 4 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value ***should be obtained between Visits S1 and S2*** and will be used to determine eligibility.

Original Text:

5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg 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.

New Text

5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and diastolic blood pressure (DBP) ≥100 mmHg 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 ***(between Visits S1 and S2***) 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.

Original Text:

14. Blood donation, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, 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.
16. Previous enrollment in a bempedoic acid clinical study.
17. Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study:
    - New or planned dose changes of systemic corticosteroids. Stable doses and topical steroids allowed.
    - Requirement for simvastatin >40 mg, mipomersen or lomitapide or apheresis therapy
    - Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
      – Hormone replacement (6 weeks prior to randomization)
      – Thyroid replacement (6 weeks prior to randomization)
      – Diabetes medications (4 weeks prior to randomization)
      – Obesity medication (3 months prior to randomization)
      – Red yeast rice extract-containing products are not allowed (2 weeks prior to screening)
18. Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
19. Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
22. Pregnant, breastfeeding, or intending to become pregnant.

New Text:

14. Blood donation, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, 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.
16. Previous enrollment in a bempedoic acid clinical study.

17. Use of any of the following drugs ~~within 3 months prior to screening~~ or a plan to use these drugs during the study:
    - New or planned dose changes of systemic corticosteroids. Stable doses ***(>4 weeks before Visit S1)*** and topical steroids allowed.
    - ~~Requirement for simvastatin >40 mg, mipomersen or lomitapide or apheresis therapy~~
    - ~~Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:~~
    - ***CETP inhibitors within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months prior to screening (Week -5, Visit S1)***
    - ***Mipomersen (6 months prior to screening, Week -5, Visit S1)***
    - ***Lomitapide (3 months prior to screening, Week -5, Visit S1)***
    - ***Apheresis (3 months prior to screening, Week -5, Visit S1)***
    - ***Simvastatin >40 mg (4 weeks prior to screening, Week -5, Visit S1)***
    - ***Red yeast rice extract -containing products are not allowed (2 weeks prior to screening, Week -5, Visit S1)***
18. ***Planned initiation of the following drugs during the clinical trial or changes prior to randomization (Day 1, Visit T1):***
    - Hormone replacement (6 weeks prior to randomization)
    - Thyroid replacement (6 weeks prior to randomization)
    - Diabetes medications (4 weeks prior to randomization)
    - Obesity medication (~~3 months~~ ***4 weeks*** prior to randomization)

      ~~Red yeast rice extract-containing products are not allowed (2 weeks prior to screening)~~
19. Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
20. Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
21. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
23. Pregnant, breastfeeding, or intending to become pregnant ***within 30 days after last dose of study drug.***
24. ***Patients who have enrolled in a study of an experimental siRNA of PCSK9 are excluded.***

CHANGE 6 SAFETY AND MONITORING REVISIONS

Location:

Section 2, Synopsis

Original Text:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is ≥25% from the patient's baseline value at Week 0 (Visit T1)

New Text:

Monitoring and Management Plans for Lipid Elevations:

Elevated LDL-C—Adjunctive Therapy:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is ***>170 mg/dL (4.4 mmol/L) and*** ≥25% from the patient's baseline value at Week 0 (Visit T1)

CHANGE 7 STATISTICAL METHODS REVISIONS

Location:

Section 2, Synopsis; Section 12.6, Secondary and Tertiary Efficacy Endpoints

Original Text:

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

Percent change from baseline to Week 24 in LDL-C; change from baseline to Weeks 12, 24, and 52 in LDL-C; percent change from baseline to Weeks 12, 24, and 52 in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and the relevant baseline as a covariate.

New Text:

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

Percent change from baseline to Week 24 in LDL-C; ***absolute*** change from baseline to Weeks 12, 24, and 52 in LDL-C; percent change from baseline to Weeks 12, 24, and 52 in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and the relevant baseline as a covariate.

Location:

Synopsis, Safety Analyses

Original Text:

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

The summarization of AEs will include treatment-emergent AEs (TEAEs), defined as AEs with an onset date on or after initiation of study treatment. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group.

New Text:

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

The summarization of AEs will include treatment-emergent AEs (TEAEs), defined as AEs with an onset date on or after initiation of study treatment. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each treatment group.

Location:

Synopsis, PK and Other biomarkers

Original Text:

PK plasma concentrations will be summarized at predose (T1) Weeks 24 and 52.

New Text:

PK plasma concentrations of ***ETC-1002 and its metabolite ESP15228*** will be summarized at ~~predose (T1)~~ Weeks 24 and 52.

CHANGE 8 MECHANISM OF ACTION 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 9 STUDY DESIGN REVISIONS

Location:

Section 2, Synopsis; Section 6.1, Overall Study Design

Original Text:

There will be no cap placed on randomization into any particular stratum. Approximately 750 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = 500), or placebo (n = 250) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (Visit T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (Visit T6).

New Text:

~~There will be no cap placed on randomization into any particular stratum.~~ Approximately ***525*** eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = ~~500~~***350***), or placebo (n = ~~250~~***175***) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (Visit T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (Visit T6). ***For patients taking simvastatin 40 mg, there will be additional clinic visits to assess safety at Weeks 16 and 28 as well as telephone visits at Weeks 20 and 32.***

CHANGE 10 CONCOMITANT MEDICATIONS REVISIONS

Location:

Section 8.2.1, Lipid-Regulating Medications and Supplements

Original Text:

Statins

- Atorvastatin (Lipitor®, Sortis®)
- Fluvastatin (Lescol®)
- Lovastatin (Mevacor®, Altoprev™)
- Pravastatin (Pravachol®)
- Pitavastatin (Livalo®, Lipostat®)
- Rosuvastatin (Crestor®)
- Simvastatin (Zocor®)

New Text:

Statins

- Atorvastatin (Lipitor®, Sortis®)
- Fluvastatin (Lescol®)
- Lovastatin (Mevacor®, Altoprev™)
- Pravastatin (Pravachol®)
- Pitavastatin (Livalo®, Lipostat®)
- Rosuvastatin (Crestor®)
- Simvastatin (Zocor®) ***(doses ≥ 40 mg are exclusionary)***

CHANGE 11 PROHIBITED MEDICATIONS REVISIONS

Location:

Section 8.2.2, Prohibited Medications

Original Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within 4 weeks prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks). Short-term intermittent use (<14 days) of pulse steroids are allowed. Topical steroids are allowed.
- Gemfibrozil (Lopid®) (as per co-administration instructions defined in the statin label)

- Cholestin (red yeast rice extract, also known as monascus purpureus extract) (2 weeks prior to screening)

New Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within ***the allotted time period*** ~~4 weeks~~ prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks). Short-term intermittent use (<14 days) of pulse steroids are allowed. Topical steroids are allowed.
- Gemfibrozil (Lopid®) (as per co-administration instructions defined in the statin label***) ≥6 weeks prior to screening (Visit S1)***
- Cholestin (red yeast rice extract, also known as monascus purpureus extract) (≥2 weeks prior to screening)
- ***CETP inhibitors within the last 2 years prior to screening (Visit S1) except for evaceptrapib within the last 3 months prior to screening (Visit S1)***
- ***Mipomersen within 6 months prior to screening (Visit S1)***
- ***Lomitapide within 3 months prior to screening (Visit S1)***
- ***Apheresis within 3 months prior to screening (Visit S1)***
- ***Simvastatin >40 mg***

CHANGE 12 ALLOWABLE MEDICATIONS REVISIONS

Location:

Section 8.2.3, Allowable Medications

Original Text:

Other concomitant medication must be stable 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 (excluding gemfibrozil)

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

- Hypertriglyceridemia therapy
- Lipid-lowering therapy, including dietary supplements and herbal remedies (except red yeast rice extract-containing products, which are exclusionary used for the purposes of lipid lowering).
- Diabetes medications

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:

Other concomitant medication***s*** must be stable ~~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 (excluding gemfibrozil)~~

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

- ~~Hypertriglyceridemia therapy~~
- ~~Lipid-lowering therapy, including dietary supplements and herbal remedies (except red yeast rice extract-containing products, which are exclusionary used for the purposes of lipid lowering).~~
- Diabetes medications

~~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 13 INVESTIGATIONAL MEDICINAL PRODUCT SUPPLY AND CONTROL REVISION

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 100 day supply increments to patients by appropriate clinical site personnel. Patients will receive one 100-day supply bottle at Week 0 (Visit T1), Week 12 (Visit T4), and two 100-day supply bottles at Week 24 (Visit T5).

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 100 day supply increments to patients by appropriate clinical site personnel. Patients will receive one 100-day supply bottle at Week 0 (Visit T1), Week 12 (Visit T4), and two 100-day supply bottles at Week 24 (Visit T5). ***At Week 12, patients will return their first bottle and tablets will***

be counted by study personnel who will then dispense a second bottle. At Week 24, tablets from the second bottle will be counted and the final 2 bottles dispensed. At Week 52, tablets will be counted by study personnel from the 2 bottles dispensed at Week 24.

CHANGE 14 STUDY PROCEDURES REVISION

Location:

Section 10.1, Informed Consent

Original Text:

The patient must be adequately informed of the nature and risks of the study and understand the informed consent document (ICD). No study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the 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 15 PROCEDURES AND SCHEDULE OF ASSESSMENTS REVISIONS

Location:

Section 10.2.1, Screening Week -5 (Visit S1; Day -35 ± 7 days)

Original Text:

10.2.1 Screening Week -5 (Visit S1; Day -35)

New Text:

10.2.1 Screening Week -5 (Visit S1; Day -35 ± *7 days)*

Original Text:

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their therapy(s) 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).

Note:

- 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 repeat lipid values will be used to determine eligibility.
- An optional visit between Visits S1 and TI may be scheduled to collect screening fasting labs in the event that the patient arrives at Visit S1 in a nonfasted state.
- An optional visit between Visits S1 and TI may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after BP medications have been adjusted, they have been on stable doses of BP medications for at least 2 weeks, and the repeat BP values (DBP and/or SBP) no longer meet exclusionary values.
- An optional visit between Visits S1 and TI may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

New Text:

Patients who meet all enrollment criteria that can be assessed at Visit S1 will be instructed to continue their therapy(s) 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).

Note:

- An optional visit approximately 1 week later MAY be completed if patient fails ~~to meet a lipid~~ ***TG*** entry criterion. If this optional visit is completed, the repeat lipid values will be used to determine eligibility.
- An optional visit between Visits S1 and ~~TI~~ ***S2*** may be scheduled to collect screening fasting labs in the event that the patient arrives at Visit S1 in a nonfasted state.
- An optional visit between Visits S1 and ~~TI~~ ***S2*** may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after BP medications have been adjusted, they have been on stable doses of BP medications for at least 2 weeks, and the repeat BP values (DBP and/or SBP) no longer meet exclusionary values.
- An optional visit between Visits S1 and ~~TI~~ ***S2*** may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

Original Text:

10.2.2 Placebo Run-in Week -4 (Visit S2; Day -28)

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

The patient will undergo the following assessments and procedures at (Visit S2)

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

New Text:

10.2.2 Placebo Run-in Week -4 (Visit S2; Day -28 ±*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

The patient will undergo the following assessments and procedures at (Visit S2)

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

Original Text:

10.2.3 Placebo Run-in Week -1 (Visit S3; Day -7)

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

- 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

New Text:

10.2.3 Placebo Run-in Week -1 (Visit S3; Day -7 ±*3 days)*

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

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

- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG); ***LDL-C must be ≥70 mg/dL (1.8 mmol/L) to be eligible***
- Conduct diet and exercise counseling

Original Text:

10.2.4 Treatment Week 0 (Visit T1; Day 1)

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 the 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.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination (PE)
- Weight
- 12-Lead electrocardiogram (ECG)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Note: Urine pregnancy test (for females of childbearing potential)
  - Coagulation in patients on vitamin K antagonists only (and repeat 3-5 days later)
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
  - Reserve sample
  - Genetic sample (optional)
- Review inclusion/exclusion criteria to establish patient eligibility

- Plasma PK
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions (one 100-day supply bottle)
- Return of placebo assessment and recording of drug compliance
- Schedule next visit

New Text:

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.*** ~~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 the 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.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints*** ~~(starting from signing of the informed consent document)~~
- Physical examination (PE)
- Weight
- 12-Lead electrocardiogram (ECG)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Note: Urine pregnancy test (for females of childbearing potential)
  - Coagulation in patients on vitamin K antagonists only (and repeat 3-5 days later)
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}

  - hs-CRP
  - ~~Reserve sample~~
  - ~~Genetic sample (optional)~~
- Review inclusion/exclusion criteria to establish patient eligibility
- ~~Plasma PK~~
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions (one 100-day supply bottle)
- Return of placebo ~~assessment~~ tablets, record compliance and ensure patient meets eligibility criteria ~~and recording of drug compliance~~
- Schedule next visit

Original Text:

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

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.3.2 for the list of the required assessments. The patient will be asked to continue to be followed for safety using the protocol-specified visit schedule. If the patient consents for follow-up, schedule the next protocol-specified visit.

Patients who do not provide consent 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 52 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 Week 4 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- Weight
- Vital signs
- Clinical 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

- Return of IMP; assessment and recording of IMP compliance
- Re-dispense IMP container from Visit T1 to patient for continued dosing and provide dosing instruction
- 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:

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

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.3.2 for the list of the required assessments. The patient will be asked to continue to be followed for safety using the protocol-specified visit schedule. ~~If the patient consents for follow-up, schedule the next protocol-specified visit.~~

Patients ~~who do not provide consent~~ ***refusing*** to continue to return to the clinic for ~~safety~~ ***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 52 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 Week 4 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints*** since last visit (ongoing)
- Weight
- Vital signs
- Clinical 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
- Return of IMP; assessment and recording of IMP compliance

- Re-dispense IMP container from Visit T1 to patient for continued dosing and provide dosing instruction
- 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.~~

Original Text:

10.2.7 Treatment Week 12 (Visit T4; 85 ±3 days)

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.3.2 for the list of the required assessments. The patient will be asked to continue to be followed for safety 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 52 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 Week 12 (Visit T4):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- Conduct diet and exercise counseling

- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP and provide dosing instructions (one 100-day supply bottle)
- 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 apoB, hs-CRP, PK samples, and 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 medications, and current health status.

New Text:

10.2.7 Treatment Week 12 (Visit T4; 85 ±3 days)

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs ***SAEs, and potential clinical endpoints*** since last visit (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP and provide dosing instructions (one 100-day supply bottle)
- 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 apoB, hs-CRP,~~

~~PK samples, and 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 medications, and current health status.~~

10.2.8 Treatment Week 16 (Visit T4.1; 112 ± 3 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be scheduled for an additional visit, Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs as well as additional assessments as described below. Should changes be noted, the procedures described in Sections 11.1.6.3.1 and 11.1.6.3.4 will apply.

- ***Concomitant and prohibited medication review (ongoing)***
- ***Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)***
- ***Clinical laboratory evaluations***
  - ***Hematology, blood chemistry, and urinalysis***

10.2.9 Treatment Week 20/Telephone Visit (Visit T4.2; 140 ± 3 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be contacted by telephone for additional Visit T4.2 to collect the following information:

- ***Concomitant and prohibited medication review (ongoing)***
- ***Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)***

Original Text:

10.2.8 Treatment Week 24 (Visit T5; 168 ±3 days)

New Text:

10.2.10 Treatment Week 24 (Visit T5; 168 ±3 days)

Original Text:

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)

  - apoB
  - HbA_{1C}
  - hs-CRP
- PK sample
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP
- Dispense IMP and provide dosing instructions (two 100 day supply 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 apoB, hs-CRP, PK samples, and 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 medications, and current health status.

New Text:

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, ***SAEs, and potential clinical endpoints*** since last visit (ongoing)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- PK sample ***before dose***
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- IWRS contact to obtain the MED ID number for IMP

- Dispense IMP and provide dosing instructions (two 100 day supply 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 apoB, hs-CRP, PK samples, and 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 medications, and current health status.~~

10.2.11 Treatment Week 28 (Visit T5.2; 196 ± 7 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be scheduled for an additional visit, Visit T5.2 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs as well as additional assessments as described below. Should changes be noted, the procedures described in Sections 11.1.6.3.1 and 11.1.6.3.4 will apply.

- ***Concomitant and prohibited medication review (ongoing)***
- ***Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)***
- ***Clinical laboratory evaluations***
  - ***Hematology, blood chemistry, and urinalysis***

10.2.12 Treatment Week 32/Telephone Visit (Visit 5.2; 224 ± 7 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be contacted by telephone for additional Visit T4.2 to collect the following information:

- ***Concomitant ad prohibited medication review (ongoing)***
- ***Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)***

Original Text:

10.2.14 Treatment Week 52/EOS (Visit T7; 365 ±7days)

Patients will undergo the following assessments and procedures at Week 52 (Visit T7), when completing an End of Study (EOS) visit, withdrawing from study (early withdrawal), or withdrawing from IMP treatment:

Patients will undergo the following assessments and procedures at Week 52 (Visit T7):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- PE

- Weight
- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- PK sample
- Reserve sample
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study).

New Text:

10.2.14 Treatment Week 52/EOS (Visit T7; 365 ±7days)

Patients will undergo the following assessments and procedures at Week 52 (Visit T7), when completing an End of Study (EOS) visit, withdrawing from study (early withdrawal), or withdrawing from IMP treatment:

Patients will undergo the following assessments and procedures at Week 52 (Visit T7):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs ***SAEs, and potential clinical endpoint*** since last visit (ongoing)
- PE
- Weight
- 12-Lead ECG
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
  - apoB
  - HbA_{1C}
  - hs-CRP
- PK sample ***before dose***

- ~~Reserve sample~~
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, early withdrawal or completed study).

CHANGE 16 SUBJECT WITHDRWAL CRITERIA REVISION

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 52 (Visit T7) to be considered as having completed participation in the study.

Patients who withdraw from IMP prior to Week 52 (Visit T7) 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).

New Text:

Patients must remain in the study until the last scheduled visit at Week 52 (Visit T7) to be considered as having completed participation in the study.

Patients who withdraw from IMP prior to Week 52 (Visit T7) 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).~~

CHANGE 17 ADDITIONAL SAMPLES REVISIONS

Location:

Section 11.1.6.1, Laboratory Parameters (Safety)

Original Text:

Table 5: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Coagulation (screening for all patients, T1 and 3-5 days after T1 in patients receiving anticoagulation therapy, only) • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • 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)	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • Reserve blood samples for potential future measurement of bempedoic acid safety or pharmacodynamic biomarkers • PK sample • Reserve genetic blood sample (optional)

[a] If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained.
[b] If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease.

New Text:

Table 5: Clinical Laboratory Parameters (Safety) (Continued)

Clinical Laboratory Test	Clinical Laboratory Test
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Coagulation (screening for all patients, T1 and 3-5 days after T1 in patients receiving anticoagulation therapy, only) • Prothrombin time (PT) • International normalized ratio (INR)
Other Screening Labs • 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)	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • ~~Reserve blood samples for potential future measurement of bempedoic acid safety or pharmacodynamic biomarkers~~ • PK sample • ~~Reserve genetic blood sample (optional~~)

[a] If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained.
[b] If HCV-AB is positive, a reflex HCV RNA will be performed to rule out active disease.

CHANGE 18 SAMPLE COLLECTION REVISIONS

Location:

Section 16.1.6.2, Sample Collection, Storage, and Shipping

Original Text:

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. For collection and processing of PK samples, please see Section 11.1.6.5 and Section 11.1.6.6. Samples will be processed by the Central Laboratory, and PK samples will be forwarded to the Bioanalytical Laboratory for analysis. Reserve samples will be stored frozen for potential future measurement of additional bempedoic acid safety and efficacy biomarkers. A reserve genetic blood sample (optional) will also be stored frozen for potential future bempedoic acid genetic analyses.

New Text:

Clinical laboratory samples will be collected by appropriate clinical site personnel and then shipped according to a separate laboratory manual provided by the Central Laboratory. For collection and processing of PK samples, please see Section 11.1.6.5 and Section 11.1.1.6. Samples will be processed by the Central Laboratory. ~~and PK samples will be forwarded to the Bioanalytical Laboratory for analysis. Reserve samples will be stored frozen for potential future measurement of additional bempedoic acid safety and efficacy biomarkers. A reserve genetic blood sample (optional) will also be stored frozen for potential future bempedoic acid genetic analyses.~~

CHANGE 19 MONITORING ABNORMAL LABS REVISIONS

Location:

Section 11.1.6.3, General Monitoring and Management of Abnormal Clinical Labs

Original Text:

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the patient, the Investigator should determine if it qualifies as an AE, and if yes, an appropriate eCRF will be completed. 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.

New Text:

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the patient, the Investigator should determine if it qualifies as an AE, and if yes, an appropriate eCRF will be completed.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- ***an action on the study drug is made as a result of the abnormality***
- ***intervention for management of the abnormality is required***
- ***at the discretion of the investigator should the abnormality be deemed clinically significant***

All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause or resolution. Specific monitoring and management guidelines for laboratories of special interest are outlined in the sections below.

CHANGE 20 MONITORING ELEVATED LIVER FUNCTION TESTS

Location:

Section 11.1.6.3.1, Monitoring and Management of Elevated Liver Function Tests

Original Text:

- If repeat LFT assessment confirms ALT and/or AST >5 × 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 × 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):

New Text:

- If repeat LFT assessment confirms ALT and/or AST >5 × 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 if deemed by the investigator.***
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further 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 if deemed by the investigator.***

CHANGE 21 MONITORING ELEVATED CREATINE KINASE

Location:

Section 11.1.6.3.4, Monitoring and Management of Elevated Creatine Kinase

Original Text:

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 × ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat CK assessment will include query for related symptoms.

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

New Text:

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 × ULN, the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

Repeat CK assessment will include query for related symptoms.

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

CHANGE 22 SAMPLE COLLECTION, BIOMARKER, AND GENETIC TESTING REVISIONS

Location:

Sections 11.1.6.6 through 11.1.6.10

Original Text:

11.1.6.6 Collection and Assessment of Pharmacokinetic Samples

Pharmacokinetic samples will be collected from patients prior to the first dose (T1), Weeks 24 and 52, for use in further developing the population PK model.

Plasma concentrations of bempedoic acid 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.

11.1.7. 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.

11.1.8. Shipment of Pharmacokinetic Samples

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

11.1.9 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.

11.1.10 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, biomarker assessment, and genetic analysis. Total whole blood volume collected over the study duration is not to exceed approximately 250 mL for each patient.

New Text:

11.1.6.6 Collection and Assessment of Pharmacokinetic Samples

Pharmacokinetic samples will be collected from patients ~~prior to the first dose (T1),~~ ***at*** Weeks 24 and 52, for use in further developing the population PK model.

Plasma concentrations of bempedoic acid 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.

~~**11.1.6.7. 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.~~

11.1.6.7~~8~~. Shipment of Pharmacokinetic Samples

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

~~**11.1.9 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.~~

11.1.6.~~8~~***10*** 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 ~~and genetic analysis~~. Total whole blood volume collected over the study duration is not to exceed approximately 250 mL for each patient.

CHANGE 23 ADVERSE EVENT REPORTING REVISIONS

Location:

11.2.3 Reporting

Original Text:

11.2.3 Reporting

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 S1 (Week -5), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

New Text:

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 to the Investigator ***through 30 days following the last dose of study drug.*** Beginning with Visit S1 (Week -5), Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF. ***Any SAE that occurs from the time of ICF through 30 days following the last dose of study drug should be reported to the Sponsor per Section 11.3.***

CHANGE 24 SAE REPORTING REVISIONS

Location:

Section 11.2.7.1, Definition of Serious Adverse Event

Original Text:

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

New Text:

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

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 non-serious 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 central (or local where appropriate) laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. For criteria of reporting abnormal lab values as AE, see Section 11.1.6.3

CHANGE 25 SAE REPORTING REVISIONS

Location:

Section 11.3, Reporting Serious Adverse Events

Original Text:

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 or study discontinuation, must be reported by the Principal Investigator or designee to the authorized Medical and Safety Services within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. For most patients this will be 30 days following their Week 52 (Visit T7) visit. 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 email or fax it to the contact information provided on the SAE form within 24 hours of becoming aware of the occurrence.

New Text:

All SAEs, regardless of relationship to study drug, occurring from the time of informed consent until 30 days following ~~study completion or study discontinuation~~, ***the last dose of IMP*** must be reported by the Principal Investigator or designee to the authorized Medical and Safety Services within 24 hours of the Principal Investigator or the clinical site becoming aware of the occurrence. For most patients this will be 30 days following their Week 52 (Visit T7) visit. 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~~ ***information in the clinical electronic data capture (EDC) database*** ~~and email or fax it to the contact information provided on the SAE form~~ within 24 hours of becoming aware of the occurrence. ***Additional information, such as diagnostic test results or hospital discharge summary can be sent via email*** [redacted] ***or via fax (*** [redacted] ***).***

CHANGE 26 PREGNANCY REPORTING REVISIONS

Location:

Section 11.3.3, Reports of Pregnancy

Original Text:

11.3.3 Reports of Pregnancy

If a female patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately. A pregnancy is not considered to be an AE or an SAE; however, it must be reported to the Sponsor / SAE designee using the Pregnancy Report Form within the same timelines as an SAE. A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to the Sponsor. Adverse events or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms. Patients who become pregnant will discontinue IMP immediately and complete the End of Study evaluations.

New Text:

If a female patient becomes pregnant during the study ***or within 30 days after the last dose of study drug,*** the investigator is to stop dosing with study drug(s) immediately. A pregnancy is not considered to be an AE or an SAE; however, it must be reported to the Sponsor / SAE designee using the ***paper*** Pregnancy Report Form within the same timelines as an SAE. A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the ***paper*** Pregnancy Outcome Report Form should be completed and reported to the Sponsor. Adverse events or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE ***CRF*** ~~or SAE forms~~. Patients who become pregnant will discontinue IMP immediately and complete the End of Study evaluations.

CHANGE 27 STATISTICAL METHODS REVISIONS

Location:

Sections 12.1, General Considerations; 12.5, Primary Endpoint; 12.6, Secondary and Tertiary Endpoints

Original Text:

12.1 General Considerations

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

New Text:

12.1 General Considerations

The statistical analyses described in this section will be performed as further outlined in a separate Statistical Analysis Plan (SAP)~~, which will be finalized prior to the first DMC assessment of safety~~. The SAP will supersede the protocol in the event of any differences

between the 2 documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

Original Text:

12.5 Primary Endpoint;

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a covariate. Baseline LDL-C is defined as the mean of the LDL-C values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the LDL-C values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Two methods for data handling will be used: the first is observed case data only, while the second will involve specification of the missing data mechanism using a pattern mixture model (PMM). The primary analysis will be that from the PMM, while the observed case analysis will be used as confirmatory. The PMM will be used to specify different imputation strategies depending on whether the patient is still on study treatment. The PMM will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Patients with missing LDL-C data at Week 12 who are no longer taking study treatment can be assumed to no longer be benefitting from study medication, and their missing value(s) can be assumed to be returning toward their baseline value. In this instance, it is reasonable to impute LDL-C values based on the patients' baseline value. Patients with missing LDL-C data at Week 12 who are still taking study treatment can be assumed to continue to benefit from study medication, and their missing value(s) can be assumed to be similar to those who remain on study treatment and have data. In this instance, it is reasonable to impute LDL-C values based on the observed values in their randomized treatment group at Week 12. To account for uncertainty, missing values will be imputed using multiple imputation.

Imputed datasets will be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a covariate. Approximately 100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

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

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

Percent change from baseline to Weeks 24 and 52 in LDL-C; change from baseline to Weeks 12, 24, and 52 in LDL-C; percent change from baseline to Weeks 12, 24, and 52, in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and the relevant baseline as a covariate. Baseline for HDL-C, non-HDL-C, TG, and TC will be defined as the mean of the lipid values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the lipid values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP will be defined as the predose Day 1/Week 0 (Visit T1) value. Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Only observed case data will be included in each analysis (no imputation will be performed for missing data). For each lipid parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For all continuous efficacy endpoints (percent change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP; change from baseline in LDL-C; to Weeks 12, 24, and 52 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.

Percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed similarly with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI, and p-value.

New Text:

12.5 Primary Endpoint;

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a

covariate. Baseline LDL-C is defined as the mean of the LDL-C values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the LDL-C values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). ***If only one value is available, then that single value will be used for baseline. 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 group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors as factors and baseline LDL-C as a covariate. Approximately 200 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. 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. Details for PMM and multiple imputation will be descried in the SAP. ~~To account for uncertainty, missing values will be imputed using multiple imputation.~~

~~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. The PMM will be used to specify different imputation strategies depending on whether the patient is still on study treatment. Patients with missing LDL-C data at Week 12 who are no longer taking study treatment can be assumed to no longer be benefitting from study medication, and their missing value(s) can be assumed to be returning toward their baseline value. In this instance, it is reasonable to impute LDL-C values based on the patients' baseline value. Patients with missing LDL-C data at Week 12 who are still taking study treatment can be assumed to continue to benefit from study medication, and their missing value(s) can be assumed to be similar to those who remain on study treatment and have data. In this instance, it is reasonable to impute LDL-C values based on the observed values in their randomized treatment group at Week 12. To account for uncertainty, missing values will be imputed using multiple imputation.~~

~~Imputed datasets will be analyzed using ANCOVA with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and baseline LDL-C as a covariate. Approximately 100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. For each type of ANCOVA (observed case; imputation via PMM), the least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.~~

12.6 Secondary and Tertiary Efficacy Endpoints

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

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

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

In general, change or percent change in lipid parameters at a given time point will be analyzed using similar ANCOVA model for the primary endpoint ~~Percent change from baseline to Weeks 24 and 52 in LDL-C; change from baseline to Weeks 12, 24, and 52 in LDL-C; percent change from baseline to Weeks 12, 24, and 52, in HDL-C, non-HDL-C, TG, TC, apoB, and hs-CRP will each be analyzed using ANCOVA~~ with treatment group, CV risk (ASCVD only; HeFH with or without ASCVD) and baseline statin intensity (high intensity, moderate intensity, low intensity) as factors and the relevant baseline as a covariate.

Baseline for HDL-C, non-HDL-C, TG, and TC will be defined as the mean of the lipid values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1). If a repeat lipid measurement is performed at Week -1 (Visit S3), then baseline will be the mean of the lipid values from the second Week -1 assessment and predose Day 1/Week 0 (Visit T1). Baseline for apoB and hs-CRP will be defined as the predose Day 1/Week 0 (Visit T1) value.

Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. ***Same imputation method described for the primary endpoint will be used for those secondary endpoints included in the step-down procedure, while only observed data analysis will be used for other secondary and tertiary endpoints.*** ~~Only observed case data will be included in each analysis (no imputation will be performed for missing data).~~ For each lipid parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

~~For all continuous efficacy endpoints (percent change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apoB, and hs-CRP; change from baseline in LDL-C; to Weeks 12, 24, and 52 as appropriate),~~

T~~t~~he 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.

Percent change from baseline to Week 24 and to Week 52 LDL-C will be analyzed similarly with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by Week 24 for the Week 24 analysis; by Week 52 for the Week 52 analysis) included in the analyses. Only observed case data will be used (no imputation for missing data). Output from each time point will include the LSM and SE for each treatment group, as well as the placebo-correct LSM, 95% CI, and p-value.

CHANGE 28 SAFETY ENDPOINTS TEXT CLARIFICATION

Location:

Section 12.8, Safety Endpoints

Original Text:

12.8 Safety Endpoints

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

The summarization of AEs will include 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.

New Text:

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

The summarization of AEs will include 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.

CHANGE 29 PHARMACOKINETICS REVISION

Location:

Section 2, Synopsis; Section 12.9, Pharmacokinetics

Original Text:

12.9 Pharmacokinetics

Trough plasma concentrations of bempedoic acid and ESP15228 will be collected and summarized from patients at predose (T1), Weeks 24 and 52 for use in further developing the population PK model.

New Text:

Trough plasma concentrations of bempedoic acid and ESP15228 will be collected and summarized from patients ***prior to dose*** at ~~predose (T1),~~ Weeks 24 and 52 for use in further developing the population PK model.

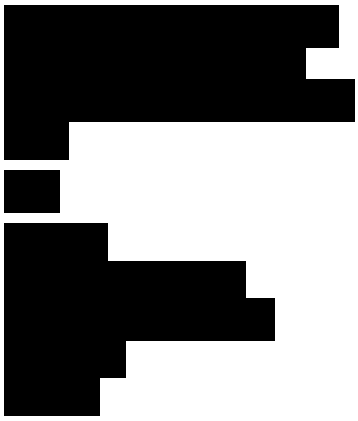
CHANGE 30 MOVED TEXT TO PHARMACY MANUAL

Location:

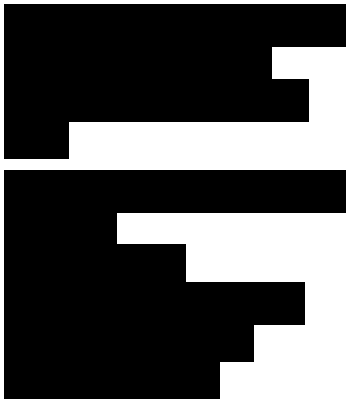
Table 4, Investigational Medicinal Products; Section 17.2, Study Administrative Structure

Original Text:

Fill/Finish Manufacturing:



Secondary Packaging/Depot for Clinical Site Drug Shipments:



New Text:

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

~~Fill/Finish Manufacturing:~~

[redacted]

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

[redacted]

CHANGE 31 SCHEDULE OF EVENTS REVISIONS

Location:

Appendix 1, Schedule of Events (Subject Visit Schedule)

Original Text:

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

		Screen	Run-in	Treatment						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5**	**T6/phone**	**T7/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**
Procedure	**Day --35**	**Day -28**	**Day -7**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**	**Day 252±7**	**Day 365 ±7**
Informed Consent	X									
Enrollment Criteria	X									
Demographics	X									
Medical History	X									
HeFH Status Determination	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X
Physical Exam				X						X
Weight[4]	X			X	X		X	X		X
Height/BMI	X									

		Screen	Run-in	Treatment						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5**	**T6/phone**	**T7/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**
Procedure	**Day --35**	**Day -28**	**Day -7**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**	**Day 252±7**	**Day 365 ±7**
12-Lead ECG[5]				X						X
Vital Signs[6]	X	X	X	X	X		X	X		X
Serology[7]	X									
Serum Pregnancy and/or FSH[8]	X									
Urine Pregnancy Test[8]				X						
TSH	X									
Clinical Safety Labs[9]	X			X	X		X	X		X
Basic Fasting Lipids[10]	X		X	X	X		X	X		X
HbA_{1C}	X			X			X	X		X
10 mL reserve sample				X						X
Genetic sample (optional)				X						
apoB				X			X			X
hs-CRP				X			X			X
Diet and exercise counseling[11]	X	X	X	X	X	X	X	X	X	X
Plasma PK				X				X		X
Establish Patient Eligibility				X						
Randomization				X						
IWRS Contact	X	X		X			X	X		X[12]
Single-Blind Drug Dispensing		X								
Double-blind Drug Dispensing[13]				X			X	X		
Drug Return/Compliance			X	X	X		X	X		X
Schedule next visit	X	X	X	X	X	X	X	X	X	

NOTE: For patients who withdraw from IMP treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

[1] An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional basic fasting (minimum of 10 hours) lipid value visit is completed, the mean of the first value and repeat lipid value will be used to determine eligibility.

[2] An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

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

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

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

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

[7] Serology for HBsAg, HCV

[8] Serum pregnancy test completed in premenopausal women only. FSH test is completed in women <55 years old and >1 year without menses. Urine pregnancy test in women of childbearing potential just prior to randomization.

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1), Baseline (Visit T1) only if on anticoagulants). Please refer to laboratory manual for detailed schedule of tests.

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

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

[12] IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

[13] Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS.

[14] If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

New Text:

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

		Screen	Run-in	Treatment*						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5**	**T6/phone**	**T7/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**
Procedure	**Day --35±*7***	**Day -28±*3***	**Day -7±*3***	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**	**Day 252±7**	**Day 365 ±7**
Informed Consent	X									
Enrollment Criteria	X									
Demographics	X									
Medical History	X									
HeFH Status Determination	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X
Physical Exam				X						X
Weight[4]	X			X	X		X	X		X
Height/BMI	X									
12-Lead ECG[5]				X						X
Vital Signs[6]	X	X	X	X	X		X	X		X
Serology[7]	X									
Serum Pregnancy and/or FSH[8]	X									
Urine Pregnancy Test[8]				X						
TSH	X									
Clinical Safety Labs[9]	X			X	X		X	X		X
Basic Fasting Lipids[10]	X		X	X	X		X	X		X
HbA_{1C}	X			X			X	X		X
~~10 mL reserve sample~~				~~X~~						~~X~~
~~Genetic sample (optional)~~				~~X~~						

apoB				X			X	***X***		X
hs-CRP				X			X	***X***		X
Diet and exercise counseling[11]	X	X	X	X	X	X	X	X	X	X
Plasma PK				~~X~~				X		X
Establish Patient Eligibility				X						
Randomization				X						
IWRS Contact	X	X		X			X	X		X[12]
Single-Blind Drug Dispensing		X								
Double-blind Drug Dispensing[13]				X			X	X		
Drug Return/Compliance			X	X	X		X	X		X
Schedule next visit	X	X	X	X	X	X	X	X	X	

NOTE: For patients who withdraw from IMP treatment~~, but consent to be followed for safety assessments and return to clinic for these visit, the~~ ***they will continue to have*** visits ~~will occur~~ according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but ***refuse to come to the clinic for assessments*** ~~consent to be followed for safety~~ assessments ***will take place*** by phone. ***T***he telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death).

~~If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.~~

**** Patients receiving simvastatin 40 mg will have clinic visits performed at Weeks 16 and 28 and telephone visits at Weeks 20 and 32. At clinic visits at Weeks 16 and 28, perform clinical safety labs as defined in Footnote 9, assess adverse events and review changes in concomitant medications. At telephone visits performed at Weeks 20 and 32, assess adverse events and review changes in concomitant medications.***

[1] An optional visit ~~approximately 1 week later MAY~~ ***between Visits S1 and S2 may*** completed if patient fails to meet a ~~lipid entry~~ ***TG*** criterion. If this optional basic fasting (minimum of 10 hours) lipid value visit is completed, the ~~mean of the first value and~~ repeat lipid value will be used to determine eligibility.

[2] An optional visit between Visits S1 and ***S2*** ~~T1~~ may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and ***S2*** ~~T1~~ may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

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

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

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

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

[7] Serology for HBsAg, HCV

[8] Serum pregnancy test completed in premenopausal women only. FSH test is completed in women <55 years old and >1 year without menses. Urine pregnancy test in women of childbearing potential just prior to randomization.

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1) ***for all patients***, Baseline (Visit T1) ***and 3-5 days after Visit T1*** only if on anticoagulants). Please refer to laboratory manual for detailed schedule of tests. ***A local laboratory may be used for assessment at 3-5 days after Visit T1***.

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

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

[12] IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

[13] Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS.

[14]If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

APPENDIX 8. SUMMARY OF CHANGES AMENDMENT 3

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-047
Study Title:	A Long-term, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients with Hyperlipidemia at High Cardiovascular Risk Not Adequately Controlled by Their Lipid-Modifying Therapy
Protocol Version Incorporating Current Summary of Changes:	Amendment 3: 09 May 2017
Preceding Protocol Version:	Amendment 2: 22 March 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 3 version and date to reflect amendment version details.
- Prohibited use of simvastatin ≥40 mg/day [redacted] The protocol has been amended to exclude patients receiving simvastatin ≥40 mg and remove study visits at Weeks 16, 20, 28, and 32 that were only for patients taking simvastatin 40 mg/day. A letter was provided to all investigators with instructions on how to proceed for enrolled patients receiving simvastatin 40 mg/day.

- Increased number of patients to be enrolled from approximately 525 to approximately 750 with 500 randomized to bempedoic acid and 250 randomized to matching placebo as was included in the original protocol and Amendment 1. The reason for the increase in patients is due to the recent decision to discontinue IMP in patients receiving simvastatin 40 mg/day across our program. Based on this decision, the safety database will be smaller than anticipated; therefore, we would like to increase the number of patients in this protocol to 750 as originally planned to ensure a robust safety database.
- Clarified that the requirement to have ≥80% treatment compliance during the Run-in Period refers to the average treatment compliance over the entire Run-in Period (compliance measured at Visits S3 and T1).
- Corrected the visit window for Week 24 within the protocol text and Appendix 1, Schedule of Events, to reflect 168 ± 7 days.
- Updated the definition of SAEs to include hospitalizations for preplanned surgeries and/or elective surgeries.

CHANGE 1 REVISION OF TITLE PAGE VERSION INFORMATION

Location:

Title Page

Original Text:

Version	Date
Amendment 1:	18 January 2017
Amendment 2:	22 March 2017

New Text:

Version	Date
Amendment 1:	18 January 2017
Amendment 2:	22 March 2017
Amendment 3:	***09 May 2017***

CHANGE 2 REVISION TO LOCATION OF SITES

Location:

Section 2, Synopsis

Original Text:

Clinical Sites: Approximately 125 sites located TBD

New Text:

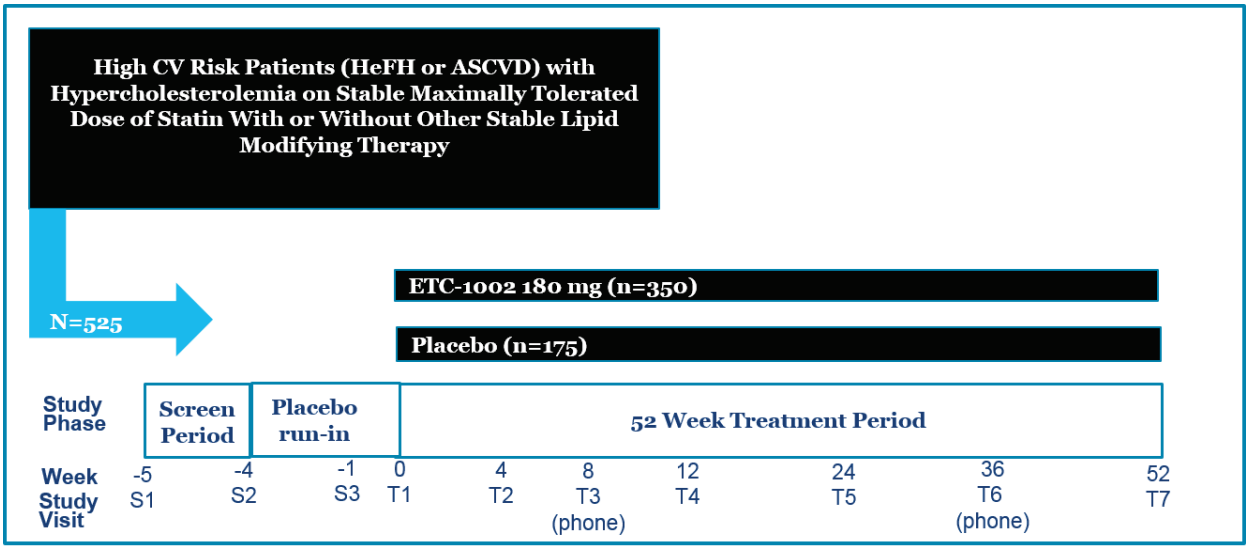
Clinical Sites: Approximately 125 sites located ~~TBD~~***in North America and Europe***

CHANGE 3 STUDY DESIGN FIGURE REVISIONS

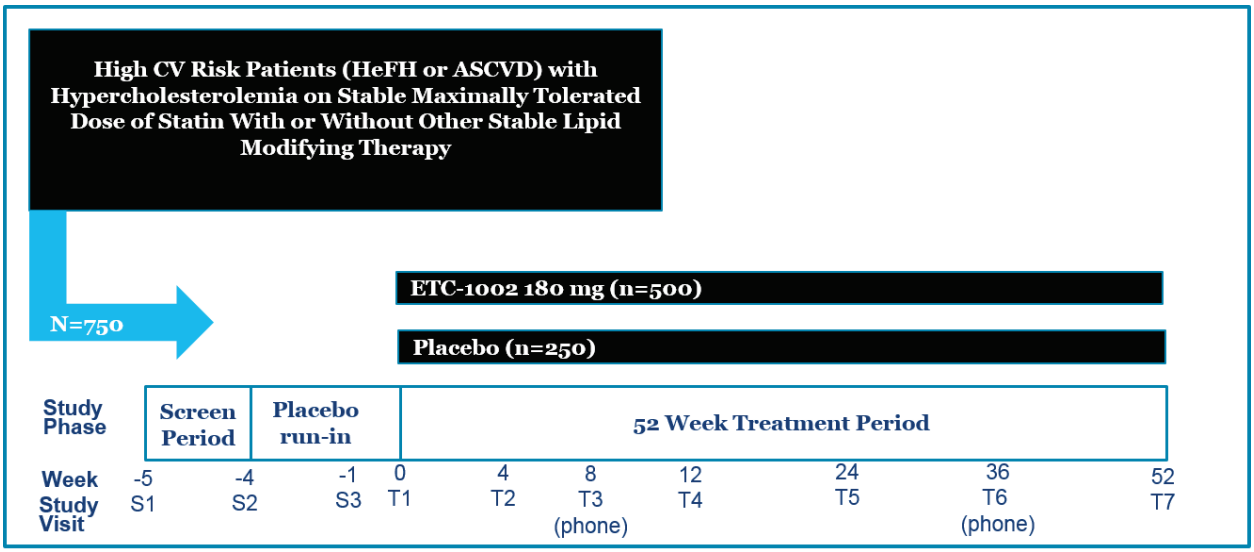
Location:

Section 2, Synopsis; 6.1 Overall Study Design

Original Text:



New Text:



CHANGE 4 SUBJECT EXCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis; Section 7.2, Subject Exclusion Criteria

Original Text:

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73m^2 at Week -5 (Visit S1) (Levey 2006). In patients taking simvastatin 40 mg, eGFR <45 mL/min/1.73 m^2 is exclusionary.

   Note: At the discretion of the investigator, the screening period may be extended up to 4 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value should be obtained between Visits S1 and S2 and will be used to determine eligibility.

New Text:

2. Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73m^2 at Week -5 (Visit S1) (Levey 2006). ~~In patients taking simvastatin 40 mg, eGFR <45 mL/min/1.73 m^2 is exclusionary.~~

   Note: At the discretion of the investigator, the screening period may be extended up to 4 weeks for a single repeat eGFR. For those patients who have a repeat eGFR, the repeat value should be obtained between Visits S1 and S2 and will be used to determine eligibility.

Original Text:

17. Use of any of the following drugs or a plan to use these drugs during the study:
    - New or planned dose changes of systemic corticosteroids. Stable doses (≥4 weeks before Visit S1) and topical corticosteroids allowed.
    - CETP inhibitors within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months prior to screening (Week -5, Visit S1)
    - Mipomersen (6 months prior to screening, Week -5, Visit S1)
    - Lomitapide (3 months prior to screening, Week -5, Visit S1)
    - Apheresis (3 months prior to screening, Week -5, Visit S1)
    - Simvastatin >40 mg (4 weeks prior to screening, Week -5, Visit S1)
    - Red yeast rice extract -containing products are not allowed (2 weeks prior to screening, Week -5, Visit S1)

New Text

17. Use of any of the following drugs or a plan to use these drugs during the study:
    - New or planned dose changes of systemic corticosteroids. Stable doses (≥4 weeks before Visit S1) and topical corticosteroids allowed.
    - CETP inhibitors within the last 2 years prior to screening (Week -5, Visit S1) except for evaceptrapib within the last 3 months prior to screening (Week -5, Visit S1)
    - Mipomersen (6 months prior to screening, Week -5, Visit S1)
    - Lomitapide (3 months prior to screening, Week -5, Visit S1)
    - Apheresis (3 months prior to screening, Week -5, Visit S1)
    - Simvastatin ~~>~~≥40 mg***/day*** (4 weeks prior to screening, Week -5, Visit S1)
    - Red yeast rice extract -containing products are not allowed (2 weeks prior to screening, Week -5, Visit S1)

CHANGE 5 INCREASE IN NUMBER OF PATIENTS TO BE ENROLLED

Location:

Section 2, Synopsis, Study Design

Original Text:

Approximately 525 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = 350), or placebo (n = 175) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (T6). Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see the Schedule of Events in Appendix 1.

New Text:

Approximately **750**~~525~~ eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = ***500***~~350~~), or placebo (n = ***250***~~175~~) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (T6). Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see the Schedule of Events in Appendix 1.

Location:

Section 2, Synopsis: Number of patients (planned)

Original Text:

Number of patients (planned): Approximately 525 adult male and female patients

New Text:

Number of patients (planned): Approximately ***750*** ~~525~~ adult male and female patients

Location:

Section 2, Synopsis: Statistical methods, Sample Size

Original Text:

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

The sample size of 350 randomized patients in the bempedoic acid 180 mg group and 175 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 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 ($\alpha = 0.05$) and a common standard deviation of 15%. The sample size of 350 randomized patients in the bempedoic acid 180 mg group and 175 randomized patients in the placebo group gives a total study sample size of 525.

New Text:

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

The sample size of ***500*** ~~350~~ randomized patients in the bempedoic acid 180 mg group and ***250*** ~~175~~ 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 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 ($\alpha = 0.05$) and a common standard deviation of 15%. The sample size of ***500*** ~~350~~ randomized patients in the bempedoic acid 180 mg group and ***250*** ~~175~~ randomized patients in the placebo group gives a total study sample size of ***750*** ~~525~~.

Location:

Section 6.1, Overall Study Design

Original Text:

Approximately 525 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = 350), or placebo (n = 175) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (Visit T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (Visit T6). For patients taking simvastatin 40 mg, there will be additional clinic visits to assess safety at Weeks 16 and 28 as well as telephone visits at Weeks 20 and 32.

New Text:

Approximately ***750*** ~~525~~ eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = ***500*** ~~350~~), or placebo (n = ***250*** ~~175~~) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (Visit T7). A phone visit will occur at Week 8 (Visit T3) and

Week 36 (Visit T6). ~~For patients taking simvastatin 40 mg, there will be additional clinic visits to assess safety at Weeks 16 and 28 as well as telephone visits at Weeks 20 and 32.~~

Location:

Section 6.2, Study Hypothesis

Original Text:

The study will assess the 12-week efficacy of bempedoic acid in decreasing LDL-C versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin alone or in combination with other lipid-lowering therapies, in patients with hyperlipidemia. The randomized, double-blind, placebo-controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that efficacy data are meaningful and interpretable. The treatment duration (52 weeks) and large patient number (n = 525) will provide robust long-term data on lipid profile, safety, and tolerability in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as bempedoic acid once daily, orally bioavailable option.

New Text:

The study will assess the 12-week efficacy of bempedoic acid in decreasing LDL-C versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin alone or in combination with other lipid-lowering therapies, in patients with hyperlipidemia. The randomized, double-blind, placebo-controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that efficacy data are meaningful and interpretable. The treatment duration (52 weeks) and large patient number (n = ***750***~~525~~) will provide robust long-term data on lipid profile, safety, and tolerability in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as bempedoic acid once daily, orally bioavailable option.

Location:

Section 6.5, Number of Patients

Original Text:

The study will enroll approximately 525 adult male and female HeFH and/or ASCVD patients with hyperlipidemia from approximately 125 clinical sites.

New Text:

The study will enroll approximately ***750***~~525~~ adult male and female HeFH and/or ASCVD patients with hyperlipidemia from approximately 125 clinical sites.

Location:

Section 12.2, Determination of Sample Size

Original Text:

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

The sample size of 350 randomized patients in the bempedoic acid 180 mg group and 175 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 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 (α = 0.05) and a common standard deviation of 15%. The sample size of 350 randomized patients in the bempedoic acid 180 mg group and 125 randomized patients in the placebo group gives a total study sample size of 525.

New Text:

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

The sample size of ***500***~~350~~ randomized patients in the bempedoic acid 180 mg group and ***250***~~175~~ 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 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 (α = 0.05) and a common standard deviation of 15%. The sample size of ***500***~~350~~ randomized patients in the bempedoic acid 180 mg group and ***250***~~175~~ randomized patients in the placebo group gives a total study sample size of ***750***~~525~~.

CHANGE 6 BASELINE STATIN DOSE CATEGORIES TABLE REVISIONS

Location:

Section 2, Synopsis; Section 6.1, Overall Study Design, Table 2

Original Text:

High Intensity Statins[a]	**Moderate Intensity Statins**	**Low Intensity Statins**[b]
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

[a] Simvastatin doses >40 mg average daily dose not allowed

[b] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and those unable to tolerate a statin at any dose

New Text:

High Intensity Statins[a]	Moderate Intensity Statins	Low Intensity Statins[b]
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin ***20 mg***~~20-40 mg~~	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

[a] Simvastatin doses ~~>~~≥40 mg***/day are*** ~~average daily dose~~ not allowed.

[b] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and those unable to tolerate a statin at any dose

CHANGE 7 SAFETY AND MONITORING REVISIONS

Location:

Section 2, Synopsis: Monitoring and Management Plans for Lipid Elevations;
Section 11.1.6.4.1, Monitoring and Management of Elevated LDL-C

Original Text:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and ≥25% from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
  - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
  - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at daily doses greater than 40 mg and the fibrate gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

New Text:

An adjunctive therapy plan is in place for those patients whose LDL-C values meet the protocol-defined LDL-C threshold criteria. Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind; however, the following thresholds have been set to notify investigators and provide an opportunity to adjust the patient's standard of care regimen.

- Beginning at Week 24 (Visit T5) visit and for the duration of the study, the central laboratory will notify the investigator when the patient's LDL-C value is >170 mg/dL (4.4 mmol/L) and ≥25% from the patient's baseline value at Week 0 (Visit T1)
- Upon receiving notification from the central laboratory that the patient has met or exceeded the threshold criteria for LDL-C, the investigator will initiate the following adjunctive therapy plan:
  - Patients will be scheduled to return to the clinic within 1 week for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria
  - After confirming that the LDL-C value meets or exceeds the threshold criteria, the investigator will adjust the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at ~~daily~~ doses ~~greater than~~ ≥40 mg***/day*** and the fibrate gemfibrozil. The patient's LDL-C will be re-evaluated at the next scheduled clinic visit as defined in the Schedule of Visits (Appendix 1).

CHANGE 8 CONCOMITANT MEDICATIONS REVISIONS

Location:

Section 8.2.1, Lipid-Regulating Medications and Supplements

Original Text:

Statins

- Atorvastatin (Lipitor®, Sortis®)
- Fluvastatin (Lescol®)
- Lovastatin (Mevacor®, Altoprev™)
- Pravastatin (Pravachol®)
- Pitavastatin (Livalo®, Lipostat®)
- Rosuvastatin (Crestor®)
- Simvastatin (Zocor®) (doses ≥40 mg are exclusionary)

New Text:

Statins

- Atorvastatin (Lipitor®, Sortis®)
- Fluvastatin (Lescol®)

- Lovastatin (Mevacor®, Altoprev™)
- Pravastatin (Pravachol®)
- Pitavastatin (Livalo®, Lipostat®)
- Rosuvastatin (Crestor®)
- Simvastatin (Zocor®) (doses ≥40 mg***/day*** are exclusionary)

Original Text:

Other

- Simvastatin/ezetimibe (Vytorin®, Inegy®)
- Atorvastatin/ezetimibe (Atozet®)

New Text:

Other

- ~~Simvastatin/ezetimibe~~***Ezetimibe/simvastatin where simvastatin is less than 40 mg/day*** (Vytorin® ***10/10 and 10/20***~~,~~ Inegy® ***10 mg/20 mg are allowed***)
- Atorvastatin/ezetimibe (Atozet®)

CHANGE 9 PROHIBITED MEDICATIONS REVISIONS

Location:

Section 8.2.2, Prohibited Medications

Original Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within the allotted time period prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks). Short-term intermittent use (<14 days) of pulse steroids are allowed. Topical steroids are allowed.
- Gemfibrozil (Lopid®) (as per co-administration instructions defined in the statin label) ≥6 weeks prior to screening (Visit S1)
- Cholestin (red yeast rice extract, also known as monascus purpureus extract) (≥2 weeks prior to screening)
- CETP inhibitors within the last 2 years prior to screening (Visit S1) except for evaceptrapib within the last 3 months prior to screening (Visit S1)
- Mipomersen within 6 months prior to screening (Visit S1)
- Lomitapide within 3 months prior to screening (Visit S1)
- Apheresis within 3 months prior to screening (Visit S1)
- Simvastatin >40 mg

New Text:

Patients will not have used medications (monotherapies or combination therapies) listed below within the allotted time period prior to screening or use these drugs during the study:

- New or planned dose changes of systemic corticosteroids. Stable doses of systemic corticosteroids at screening are allowed (≥4 weeks). Short-term intermittent use (<14 days) of pulse steroids are allowed. Topical steroids are allowed.
- Gemfibrozil (Lopid®) (as per co-administration instructions defined in the statin label) ≥6 weeks prior to screening (Visit S1)
- Cholestin (red yeast rice extract, also known as monascus purpureus extract) (≥2 weeks prior to screening)
- CETP inhibitors within the last 2 years prior to screening (Visit S1) except for evaceptrapib within the last 3 months prior to screening (Visit S1)
- Mipomersen within 6 months prior to screening (Visit S1)
- Lomitapide within 3 months prior to screening (Visit S1)
- Apheresis within 3 months prior to screening (Visit S1)
- Simvastatin ~~>~~≥40 mg***/day***
- ***Ezetimibe/simvastatin where simvastatin doses are ≥40 mg/day (Vytorin® 10/40 and 10/80 and Inegy® 10 mg/40 mg and 10 mg/80 mg are exclusionary)***

CHANGE 10 TREATMENT COMPLIANCE REVISIONS

Location:

Section 8.3, Treatment Compliance

Original Text:

Screening Compliance

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

Placebo Run-in and Treatment Period Adherence

At Week -1 (S3) visit in the placebo run-in period and at each of the subsequent patient visits, designated clinical site staff will assess patient for placebo and/or 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. 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. However, patients with ≤80% adherence and/ or who experienced a study drug-related AE, will not go onto randomization.

New Text:

Screening Compliance

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

Placebo Run-in and Treatment Period Adherence

At Week -1 (S3) visit in the placebo run-in period and at each of the subsequent patient visits, designated clinical site staff will assess patient for placebo and/or 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. 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. However, patients with ≤80% adherence ***over the entire Run-in Period*** and/ or who experienced a study drug-related AE, will not go onto randomization.

CHANGE 11 PROCEDURES AND SCHEDULE OF ASSESSMENTS REVISIONS

Location:

Section 10.2.8, Treatment Week 16 (Visit T4.1; 112 ± 3 days) Only for Patients Taking Simvastatin 40 mg

Original Text:

10.2.8 Treatment Week 16 (Visit T4.1; 112 ± 3 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be scheduled for an additional visit, Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs as well as additional assessments as described below. Should changes be noted, the procedures described in Sections 11.1.6.3.1 and 11.1.6.3.4 will apply.

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)
- Clinical laboratory evaluations
  - Hematology, blood chemistry, and urinalysis

New Text

~~**10.2.8 Treatment Week 16 (Visit T4.1; 112 ± 3 days) Only for Patients Taking Simvastatin 40 mg**~~

~~Patients taking an average daily dose of simvastatin 40 mg will be scheduled for an additional visit, Visit T4.1 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs as well as additional assessments as described below. Should changes be noted, the procedures described in Sections 11.1.6.3.1 and 11.1.6.3.4 will apply.~~

- ~~Concomitant and prohibited medication review (ongoing)~~
- ~~Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)~~
- ~~Clinical laboratory evaluations~~
  - ~~Hematology, blood chemistry, and urinalysis~~

Original Text:

10.2.9 Treatment Week 20/Telephone Visit (Visit T4.2; 140 ± 3 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be contacted by telephone for additional Visit T4.2 to collect the following information:

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)

New Text:

~~**10.2.9 Treatment Week 20/Telephone Visit (Visit T4.2; 140 ± 3 days) Only for Patients Taking Simvastatin 40 mg**~~

~~Patients taking an average daily dose of simvastatin 40 mg will be contacted by telephone for additional Visit T4.2 to collect the following information:~~

- ~~Concomitant and prohibited medication review (ongoing)~~
- ~~Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)~~

Original Text:

10.2.10 Treatment Week 24 (Visit T5; 168 ±3 days)

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section 10.2.14 for the list of the required assessments. The patient will be asked to continue to be followed for safety

New Text:

10.2.8~~10.2.10~~ Treatment Week 24 (Visit T5; 168 *±7 days* ~~± 3 days~~)

If the patient is withdrawing early from the study at this visit, proceed to Section 10.3.2 for the list of the required assessments.

If the patient is withdrawing from IMP treatment at this visit, proceed to Section ~~10.2.14~~***10.2.10*** for the list of the required assessments. The patient will be asked to continue to be followed for safety

Original Text:

10.2.11 Treatment Week 28 (Visit T5.2; 196 ± 7 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be scheduled for an additional visit, Visit T5.2 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs as well as additional assessments as described below. Should changes be noted, the procedures described in Sections 11.1.6.3.1 and 11.1.6.3.4 will apply.

- Concomitant and prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)
- Clinical laboratory evaluations
  - Hematology, blood chemistry, and urinalysis

New Text:

~~10.2.11 Treatment Week 28 (Visit T5.2; 196 ± 7 days) Only for Patients Taking Simvastatin 40 mg~~

~~Patients taking an average daily dose of simvastatin 40 mg will be scheduled for an additional visit, Visit T5.2 for clinical safety laboratory evaluations specifically to monitor changes in CPK and LFTs as well as additional assessments as described below. Should changes be noted, the procedures described in Sections 11.1.6.3.1 and 11.1.6.3.4 will apply.~~

- ~~Concomitant and prohibited medication review (ongoing)~~
- ~~Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)~~
- ~~Clinical laboratory evaluations~~
  - ~~Hematology, blood chemistry, and urinalysis~~

Original Text:

10.2.12 Treatment Week 32/Telephone Visit (Visit 5.2; 224 ± 7 days) Only for Patients Taking Simvastatin 40 mg

Patients taking an average daily dose of simvastatin 40 mg will be contacted by telephone for additional Visit T4.2 to collect the following information:

- Concomitant ad prohibited medication review (ongoing)
- Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)

New Text:

~~**10.2.12 Treatment Week 32/Telephone Visit (Visit 5.2; 224 ± 7 days) Only for Patients Taking Simvastatin 40 mg**~~

~~Patients taking an average daily dose of simvastatin 40 mg will be contacted by telephone for additional Visit T4.2 to collect the following information:~~

- ~~Concomitant ad prohibited medication review (ongoing)~~
- ~~Assess AEs, SAEs, and potential clinical endpoints since last visit (ongoing)~~

CHANGE 12 DEFINITION OF SAES AND OUTCOMES NOT QUALIFYING AS SERIOUS ADVERSE EVENT CHANGES

Location:

Section 11.2.7.1, Definition of Serious Adverse Event; Section 11.2.7.2, Definition of Outcomes not Qualifying as Serious Adverse Events

Original Text:

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.

New Text:

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.

Original Text:

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

New Text:

11.2.7.2 ~~Definition of Serious Adverse Event~~ Events ~~or Outcomes~~ not Qualifying as Serious Adverse Events

The following ~~are~~***is*** not considered ***an*** SAE~~s~~ and therefore do***es*** 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

CHANGE 13 SCHEDULE OF EVENTS REVISIONS

Location:

Appendix 1, Schedule of Events (Subject Visit Schedule)

Original Text:

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

	Screen	Run-in		Treatment*						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5**	**T6/phone**	**T7/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**
Procedure	**Day --35± 7**	**Day -28± 3**	**Day -7± 3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day 169±7**	**Day 252±7**	**Day 365 ±7**
Informed Consent	X									
Enrollment Criteria	X									
Demographics	X									
Medical History	X									
HeFH Status Determination	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X
Physical Exam				X						X
Weight[4]	X			X	X		X	X		X
Height/BMI	X									
12-Lead ECG[5]				X						X
Vital Signs[6]	X	X	X	X	X		X	X		X
Serology[7]	X									
Serum Pregnancy and/or FSH[8]	X									
Urine Pregnancy Test[8]				X						
TSH	X									
Clinical Safety Labs[9]	X			X	X		X	X		X
Basic Fasting Lipids[10]	X		X	X	X		X	X		X
HbA_{1C}	X			X			X	X		X
apoB				X			X	X		X
hs-CRP				X			X	X		X
Diet and exercise counseling[11]	X	X	X	X	X	X	X	X	X	X
Plasma PK								X		X
Establish Patient Eligibility				X						
Randomization				X						
IWRS Contact	X	X		X			X	X		X[12]
Single-Blind Drug Dispensing		X								
Double-blind Drug Dispensing[13]				X			X	X		
Drug Return/Compliance			X	X	X		X	X		X
Schedule next visit	X	X	X	X	X	X	X	X	X	

NOTE: For patients who withdraw from IMP treatment, they will continue to have visits according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but refuse to come to the clinic for assessments, assessments will take place by phone. The telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death).

* Patients receiving simvastatin 40 mg will have clinic visits performed at weeks 16 and 28 and telephone visits at Weeks 20 and 32. At clinic visits at Weeks 16 and 28, perform clinical safety labs as defined in Footnote 9, assess adverse events and review changes in concomitant medications. At telephone visits performed at Weeks 20 and 32, assess adverse events and review changes in concomitant medications.

[1] An optional visit between Visits S1 and S2 may be completed if patient fails to meet TGTG entry criterion. If this optional basic fasting (minimum of 10 hours) lipid value visit is completed, the repeat lipid value will be used to determine eligibility.

[2] An optional visit between Visits S1 and S2 may be completed if the patient's DBP and/or SBP meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. An optional visit between Visit S1 and S2 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

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

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

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

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

[7] Serology for HBsAg, HCV

[8] Serum pregnancy test completed in premenopausal women only. FSH test is completed in women <55 years old and >1 year without menses. Urine pregnancy test in women of childbearing potential just prior to randomization.

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Coagulation is included at Screening (Visit S1) for all patients, Baseline (Visit T1) and 3-5 days after Visit T1 only if on anticoagulants). Please refer to laboratory manual for detailed schedule of tests. A local laboratory may be used for assessment at 3-5 days after Visit T1.

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

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

[12] IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

[13] Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS.

[14] If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events

New Text:

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

	Screen	Run-in		Treatment±						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/phone**	**T4**	**T5**	**T6/phone**	**T7/EOS[3]**
Week	**Wk -5**	**Wk -4**	**Wk -1**	**Wk 0**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**
Procedure	**Day –35± 7**	**Day -28± 3**	**Day -7± 3**	**Day 1**	**Day 29±3**	**Day 57±3**	**Day 85±3**	**Day *168*~~169~~ ±7**	**Day 252±7**	**Day 365 ±7**
Informed Consent	X									
Enrollment Criteria	X									
Demographics	X									
Medical History	X									
HeFH Status Determination	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X	X	X
Physical Exam				X						X
Weight[4]	X			X	X		X	X		X
Height/BMI	X									
12-Lead ECG[5]				X						X
Vital Signs[6]	X	X	X	X	X		X	X		X
Serology[7]	X									
Serum Pregnancy and/or FSH[8]	X									
Urine Pregnancy Test[8]				X						
TSH	X									
Clinical Safety Labs[9]	X			X	X		X	X		X
Basic Fasting Lipids[10]	X		X	X	X		X	X		X
HbA_{1C}	X			X			X	X		X
apoB				X			X	X		X
hs-CRP				X			X	X		X
Diet and exercise counseling[11]	X	X	X	X	X	X	X	X	X	X
Plasma PK								X		X
Establish Patient Eligibility				X						
Randomization				X						
IWRS Contact	X	X		X			X	X		X[12]
Single-Blind Drug Dispensing		X								
Double-blind Drug Dispensing[13]				X			X	X		
Drug Return/Compliance			X	X	X		X	X		X
Schedule next visit	X	X	X	X	X	X	X	X	X	

NOTE: For patients who withdraw from IMP treatment, they will continue to have visits according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories (except for apoB and hs-CRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP treatment, but refuse to come to the clinic for assessments, assessments will take place by phone. The telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death).

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

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