BEMPEDOIC ACID (ETC-1002)

1002-038

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TRIPLET THERAPY WITH BEMPEDOIC ACID (ETC-1002) 180 MG, EZETIMIBE 10 MG, AND ATORVASTATIN 20 MG IN PATIENTS WITH ELEVATED LDL-C

Study Phase:	2
IND Number:	106,654
EudraCT Number:	N/A
Indication:	Treatment of hyperlipidemia
Investigators:	Approximately 20 sites located in US
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108 Phone: 1-734-887-3903 Fax: 1-734-913-5344
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Version	Date
Original Protocol:	11 November 2016

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2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.

Name of Investigational Products:

Bempedoic acid (ETC-1002) film-coated tablets

Ezetimibe overencapsulated tablets

Atorvastatin overencapsulated tablets

Name of Active Ingredients:

Bempedoic acid (ETC-1002)

Ezetimibe

Atorvastatin

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Triplet Therapy with Bempedoic Acid (ETC-1002) 180 mg, Ezetimibe 10 mg, and Atorvastatin 20 mg in Patients with Elevated LDL-C

Study Number: 1002-038

Phase of Development: 2

Clinical Sites: Approximately 20 sites located in United States (US)

Primary Objective:

- To assess the low-density lipoprotein cholesterol (LDL-C) lowering effect of triplet therapy with bempedoic acid (ETC-1002) 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg versus placebo administered daily for 6 weeks in patients with elevated LDL-C

Secondary Objectives:

- To assess the effect of triplet therapy versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (ApoB), high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C)
- To assess the effect of triplet therapy versus placebo on percent of patients achieving LDL-C level <70 mg/dL
- To assess the effect of triplet therapy versus placebo on percent of patients achieving LDL-C reduction ≥50%
- To assess the safety and tolerability of triplet therapy versus placebo

Study Hypothesis:

The clinical hypothesis for this study is that triplet therapy with bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg will significantly reduce LDL-C in patients treated daily for 6 weeks compared to placebo.

Endpoints:

The following endpoints will be used to evaluate the objectives of the study.

Primary endpoint:

- Percent change from baseline to Week 6 in LDL-C

Secondary endpoints:

- Percent change from baseline to Week 6 in non-HDL-C, TC, ApoB, hs-CRP, TG, and HDL-C
- Percent of patients with LDL-C <70 mg/dL at Week 6
- Percent of patients with LDL-C reduction ≥50% from baseline to Week 6

Safety Endpoints:

- Subject incidence of adverse events (AEs)
- Clinical safety laboratory (including hematology, blood chemistry, and urinalysis) results
- Vital signs and physical examination (PE) findings

Study Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study. Patients will initially undergo screening at Week -6 (Visit S1). Eligible patients will begin washout of all LDL-C lowering drugs and nutritional supplements at least 5 weeks prior to randomization. Patients will return at Week -1 (Visit S2) for lipid and/or other assessments. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel and considered screen failures. At Week 0 (Visit T1), approximately 60 patients will be randomized in a ratio of 2:1 to receive either triplet therapy (bempedoic acid 180 mg + ezetimibe 10 mg + atorvastatin 20 mg) or placebo once daily for 6 weeks. Randomized patients will return for clinic visits at Week 3 (Visit T2), and Week 6 (Visit T3).

Number of Patients (Planned): Approximately 60 adult male and female patients.

Duration of Treatment: Total treatment duration will be 12 weeks (6 weeks screening and 6 weeks treatment) with the option to extend screening by 1 additional week.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

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 -6 (Visit S1);
3. Fasting calculated LDL-C between 130-189 mg/dL at Week -1 (Visit S2) following washout of all LDL-C-lowering drugs and nutritional supplements;

   Note: LDL-C may be repeated 1 time with the screening period extended up to 1 week. 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.
4. Patient is sufficiently stable and suitable to undergo washout of all LDL-C-lowering drugs and nutritional supplements for 12 weeks (with potential for 1 week extension) based on Investigator assessment;
5. Men and nonpregnant, nonlactating women. Women must be one of the following:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      i. ≥55 years, or
      ii. <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation, or
   c. Women of childbearing potential willing to use one acceptable method of birth control during the study and for 30 days after the end of treatment including:
      i. birth control medications,

ii. placement of an intrauterine device with or without hormones,
iii. barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly,
iv. vasectomized male partner who is the sole partner for this patient,
v. 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.

Exclusion Criteria:

1. Body mass index (BMI) >50 kg/m^2;
2. History of documented clinically significant cardiovascular disease including, but not limited to:
   a. Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease,
   b. Uncontrolled hypertension, defined as sitting mean systolic blood pressure (SBP) ≥160 mm Hg and/or diastolic blood pressure (DBP) ≥100 mm Hg after sitting quietly for 5 minutes.

      Note: At the discretion of the investigator, a single repeat sitting mean SBP and DBP may be completed at a separate visit. For those patients who have repeat sitting mean SBP and DBP assessment, the repeat values will be used to determine eligibility.
   c. An arrhythmia requiring medical intervention,
   d. Abdominal aortic aneurysm,
   e. New York Heart Association (NYHA) Class III and IV heart failure;
3. Fasting TG >400 mg/dL at Week -1 (S2);

   Note: TG may be repeated 1 time with the screening period extended up to 1 week. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.
4. History of type 1 or type 2 diabetes or fasting glucose >125 mg/dL at Week -6 (Visit S1);
5. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -6 (Visit S1);
6. Liver disease or dysfunction, including:
   a. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -1 (Visit S2), or
   b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥2 × ULN at Week -6 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

   Note: At the discretion of the investigator, a single repeat of ALT, AST, and/or TB may be completed. For those patients who have a repeat ALT, AST, and/or TB, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) is negative, the patient can be enrolled.
7. Renal dysfunction or glomerulonephritis, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min at Week -6 (Visit S1);

   Note: At the discretion of the investigator, a single repeat of eGFR may be completed. For those

patients who have a repeat eGFR, the repeat value will be used to determine eligibility;

8. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption;
9. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL at Week -6 (Visit S1);
10. 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;
11. Unexplained creatine kinase (CK) >3 × ULN at any time prior to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization;
12. History of drug or alcohol abuse within the last 2 years or reported current consumption of >14 alcoholic drinks/week, or any illicit drug use, history of amphetamine and derivatives abuse or cocaine abuse. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator;
13. Blood donation, participation in a multiple blood draws, clinical study, major trauma, blood transfusion or surgery with or without blood loss within 30 days prior to randomization;
14. Use of any experimental or investigational drugs within 30 days prior to screening;
15. Previous enrollment in a bempedoic acid clinical study;
16. Use of these prohibited drugs and/or nutritional supplements prior to randomization or planned use during the study:
    a. LDL-C lowering drugs and/or nutritional supplements (within 5 weeks prior to randomization),
    b. Probenecid or cyclosporine (within 2 weeks prior to randomization),
    c. Potent CYP3A4 inhibitors including amiodarone, azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), bosentan, clarithromycin, cobicistat, conivaptan, danazol, daptomycin, diltiazem, domperidone, erlotinib, erythromycin, fusidic acid, mibefradil, nefazodone, piperaquine, protease inhibitors (atazanavir, boceprevir, darunavir, delavirdine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir), quinupristin/dalfopristin, telithromycin, verapamil (within 2 weeks prior to randomization),
    d. Systemic corticosteroids (topical corticosteroids are allowed; within 5 weeks prior to randomization);
17. Planned initiation or dosing changes of these allowed drugs prior to or during the study:
    a. Hormone replacement (within 5 weeks prior to randomization),
    b. Thyroid replacement (within 5 weeks prior to randomization),
    c. Obesity medication (within 3 months prior to randomization);
18. 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;
19. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or any Sponsor personnel.

Investigational Medicinal Product, Dosage and Mode of Administration:

- Bempedoic acid 180-mg tablets and matching placebo
- Ezetimibe 10-mg overencapsulated tablets and similarly matching placebo capsules
- Atorvastatin 20-mg overencapsulated tablets and similarly matching placebo capsules

Investigational medicinal product (IMP) will be ingested once daily with or without food.

Non-Investigational Medicinal Product

All other background drugs will be administered as prescribed by a physician

Statistical Methods:

Sample Size

[redacted]

Analysis Populations

The modified Intent-to-Treat (mITT) population, used for all of the efficacy analyses, is defined as all randomized patients who received at least 1 dose of study drug and have a baseline assessment and at least 1 postbaseline assessment, excluding any assessment taken more than 2 days after a dose of study drug.

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 IMP and 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 and Secondary Efficacy Analysis

The primary efficacy endpoint is the percent change from baseline to Week 6 in LDL-C. Baseline is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1). An analysis of covariance (ANCOVA) with treatment group as factor and baseline LDL-C as covariate will be performed to compare triplet therapy versus placebo for the primary endpoint using the mITT population. Missing values at Week 6 will be imputed using the last observation carried forward (LOCF) procedure (only post baseline values will be carried forward). 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 efficacy endpoints, which include the percent change from baseline to Week 6 in additional lipid and cardiometabolic biomarkers, will be analyzed in a similar manner as the primary efficacy endpoint. Baseline for non-HDL-C, HDL-C, TC, and TG is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1), while baseline for ApoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value.

Statistical testing of primary and secondary efficacy endpoints will be 2-sided and conducted at the 5% level of significance with no adjustment for multiple comparisons.

Safety Analyses

Descriptive summary will be provided for safety endpoints.

The summarization of AEs will include only treatment-emergent AEs (TEAEs). TEAEs and serious adverse events (SAEs) will be summarized by system organ class (SOC), severity, and relationship to IMP for each treatment group. Deaths and withdrawal from the IMP or study due to AEs will each be summarized by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, glucose, and urinalysis; PE

findings; vital signs; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each post baseline time point.

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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
ACSVL1	Very long-chain acyl-CoA synthetase 1
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
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CRF	Case report form
CRO	Contract research organization
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram

Abbreviation or Specialist Term	Explanation
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-ABVivi	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
LOCF	Last observation carried forward
LSM	Least squares mean
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
mITT	Modified Intent-to-Treat
MRI	Magnetic resonance imaging

Abbreviation or Specialist Term	Explanation
Na	Sodium
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PCSK9	Proprotein convertase subtilisin kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
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
SUSAR	Suspected and unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

Bempedoic acid (ETC-1002) is an oral, first-in class, small molecule designed to lower low-density lipoprotein cholesterol (LDL-C). It inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid, like both statins and ezetimibe, up-regulates LDL-C receptors. However, unlike statins, bempedoic acid does not inhibit cholesterol synthesis in muscle tissue, therefore it is anticipated that negative muscle-related adverse effects associated with statin use may be avoided by use of bempedoic acid.

Hypercholesterolemic patients have several therapeutic options to lower LDL-C. Statin and nonstatin therapies that lower LDL-C via upregulation of LDL receptors are associated with reduced cardiovascular disease (CVD) risk. Bempedoic acid 180 mg, atorvastatin 20 mg, and ezetimibe 10 mg work by divergent mechanisms to lower LDL-C via up-regulation of LDL receptors. This Phase 2 study in patients with elevated LDL-C is being conducted to characterize the magnitude of LDL-C lowering achievable with this oral triplet therapy.

4.1. Cardiovascular Disease and LDL-C-Lowering Drugs

Despite aggressive interventional and pharmacologic therapies, CVD is the number 1 cause of death globally (WHO 2015). The Global Burden of Disease study estimated that 29.6% of all deaths worldwide (approximately 15.6 million deaths) were caused by CVD 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 CVD daily, an average of 1 death every 40 seconds (Mozffarian 2015). Of great concern, approximately 155,000 Americans dying from CVD are less than 65 years of age (Mozffarian 2015). In Europe, CVD remains the most common cause of deaths, resulting in almost 2 times as many deaths as cancer (Townsend 2015).

Elevated LDL-C is a major modifiable risk factor for the development of atherosclerosis and CVD (Sharrett 2001). Evidence supporting LDL-C as a therapeutic target and surrogate for cardiovascular (CV) outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, and 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 mechanism for LDL-C lowering (Kathiresan 2008; Baigent 2010; Robinson 2005; Stamler 1986, Silverman 2016). A published patient-level meta-analysis including 26 statin trials and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes (Baigent 2010). This analysis showed that a 1 mmol/L (~39 mg/dL) reduction in LDL-C was associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. More recently, a meta-analysis in 312,175 patients from 49 trials assessed the relationship between LDL-C reduction and CV outcomes when LDL-C reduction was due to statin therapy versus established nonstatin interventions that work primarily by upregulation of the LDL receptor such as diet, bile acid sequestrants, ileal bypass, and ezetimibe (Silverman 2016). This meta-analysis reported that the relationship between LDL-C reduction and CV outcomes was similar regardless of whether LDL-C reduction was

derived from statin therapy or nonstatin interventions that upregulate the LDL receptor (Silverman 2016). Thus, LDL-C lowering via upregulation the LDL receptor is largely accepted as a valid surrogate endpoint of CV risk reduction by clinicians and regulatory authorities (Stone 2013).

Statins are central to the LDL-C-lowering strategy and are supported by a large body of data demonstrating robust effectiveness in lowering LDL-C and reducing the risk of CVD (Waters 2006, Grundy 2004). However, there is increasing awareness of the limitations and risks of statin use. Many individuals at risk for CVD fail to achieve LDL-C goals (Martin 2013, Virani 2011). In 2011, the Food and Drug Administration (FDA) mandated safety-labeling changes limiting the use of high dose (80 mg) simvastatin due to safety concerns of muscle injury or myopathy (Egan 2011). Although myopathy events are rare, a more widespread problem is various muscle side effects such as pain and weakness, particularly at high doses, leading to poor tolerability and lack of persistence on statin therapy (Cohen 2012).

Other than statins, only a few drugs are approved to lower LDL-C. Although LDL-C lowering is robust with proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, use of these drugs is limited by mode of administration and other accessibility issues. The oral drug ezetimibe, an intestinal cholesterol absorption inhibitor, lowers LDL-C by 18% in patients with primary hyperlipidemia (Knopp 2003). Other oral LDL-C-lowering therapies include colesevelam, a bile acid sequestrant that lowers LDL-C by up to 18% but is limited by considerable gastrointestinal side effects (Insull 2001), while extended-release niacin in doses up to 2 g lowers LDL-C by up to 17% (Goldberg 1998). Finally, fenofibrate, an activator of peroxisome proliferator-activated receptor alpha, lowers LDL-C by approximately 20% in patients with hypercholesterolemia (Knopp 1987), but may substantially increase LDL-C in patients with hypertriglyceridemia.

An increasing body of evidence suggests that the absolute amount of LDL-C lowering is proportional to CVD risk reduction in statin and nonstatin therapies that lower LDL-C via upregulation of LDL receptors. Bempedoic acid, atorvastatin, and ezetimibe are oral therapies that work by divergent mechanisms to lower LDL-C via up-regulation of LDL receptors. The magnitude of LDL-C lowering that can be achieved by concurrent administration of these oral therapies is unknown.

4.2. Background on Bempedoic Acid

4.2.1. Mechanism of Action

Bempedoic acid is a first-in-class small molecule that decreases cholesterol synthesis in the liver. Bempedoic acid is a prodrug that requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA. ETC-1002-CoA inhibits ACL, an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Like statins, bempedoic acid decreases liver cholesterol synthesis, which results in increased LDL receptor activity and LDL particle clearance from the blood.

Both ETC-1002-CoA (via ACL inhibition) and statins (via HMG-CoA reductase inhibition) inhibit cholesterol synthesis in the liver, but an important differentiating feature is that unlike statins, bempedoic acid is inactive in skeletal muscle. This is consistent with the absence of ACSVL1 (the synthetase required to activate bempedoic acid to ETC-1002-CoA and inhibit

ACL) expression in muscle tissue. Evidence suggests that muscle-related adverse effects associated with statin use is a result of HMG-CoA reductase inhibition directly in skeletal muscle leading to a reduction of several downstream biological intermediates within the cholesterol synthesis pathway important for muscle cell function. Since bempedoic acid is not activated to ETC-1002-CoA and does not inhibit cholesterol synthesis in muscle tissue, it is anticipated that negative muscle-related adverse effects associated with statin use may be avoided by use of bempedoic acid. The long-term safety of bempedoic acid and its metabolites regarding human skeletal muscle is not yet established.

4.2.2. Nonclinical Experience

[redacted]

4.2.3. Previous Human Experience

[redacted]

[redacted]

4.2.4. Dose Selection

[redacted]

[redacted]

4.3. Background on Ezetimibe

Please see the ezetimibe label.

4.4. Background on Atorvastatin

Please see the atorvastatin label.

4.5. Risk Benefit Summary

To date, the nonclinical and clinical data indicate that bempedoic acid 180 mg has a favorable risk-benefit profile. The ability of bempedoic acid to achieve clinically meaningful LDL-C lowering while demonstrating a favorable tolerability profile in a variety of patient populations supports continued development of bempedoic acid in Phase 3 studies.

Several Phase 2 clinical studies have assessed the safety and efficacy of bempedoic acid as add-on to statins or in combination with ezetimibe. These studies showed significant LDL-C lowering and a favorable safety profile. The LDL-C lowering efficacy and safety of triplet therapy with bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg has not previously been assessed. That is the purpose of this study.

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

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Objectives

5.1.1. Primary Objective

The primary objective is to assess the LDL-C lowering efficacy of triplet therapy with bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg versus placebo administered daily for 6 weeks in patients with elevated LDL-C.

5.1.2. Secondary Objectives

- To assess the effect of triplet therapy versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (ApoB), high-sensitivity C-reactive protein (hs-CRP), TG, and HDL-C
- To assess the effect of triplet therapy versus placebo on percent of patients achieving LDL-C level <70 mg/dL
- To assess the effect of triplet therapy versus placebo on percent of patients achieving LDL-C reduction ≥50%
- To assess the safety and tolerability of triplet therapy versus placebo

5.2. Study Endpoints

The following endpoints will be used to evaluate the objectives of the study.

5.2.1. Primary Endpoint

- Percent change from baseline to Week 6 in LDL-C

5.2.2. Secondary Endpoints

- Percent change from baseline to Week 6 in non-HDL-C, TC, ApoB, hs-CRP, TG, and HDL-C
- Percent of patients with LDL-C <70 mg/dL at Week 6
- Percent of patients with LDL-C reduction ≥50% from baseline to Week 6

5.2.3. Safety Endpoints

- Subject incidence of adverse events
- Clinical safety laboratory (including hematology, blood chemistry, and urinalysis) results
- Vital signs and physical examination (PE) findings

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study. Patients will initially undergo screening at Week -6 (Visit S1). Eligible patients will begin washout of all LDL-C-lowering drugs and nutritional supplements at least 5 weeks prior to randomization. Patients will return at Week -1 (S2) for lipid and/or other assessments. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel and considered screen failures. At Week 0 (Visit T1), approximately 60 patients will be randomized in a ratio of 2:1 to receive either triplet therapy (bempedoic acid 180 mg + ezetimibe 10 mg + atorvastatin 20 mg) or placebo once daily for 6 weeks. Randomized patients will return for clinic visits at Week 3 (Visit T2) and Week 6 (Visit T3).

For details of study assessments, see the Schedule of Events in Appendix 1.

6.2. Study Hypothesis

The clinical hypothesis for this study is that triplet therapy with bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg will significantly reduce LDL-C in patients treated daily for 6 weeks versus placebo.

6.3. Estimated Study Duration and Period

Total treatment duration will be 12 weeks (6 weeks screening and 6 weeks treatment) with the option to extend screening by 1 additional week.

6.4. Number of Centers

Up to approximately 20 centers in the US will participate in this. Additional sites may be invited to participate to ensure study timelines are met.

6.5. Number of Patients

The study will enroll approximately 60 adult male and female patients.

7. SELECTION OF PATIENTS

7.1. Subject Inclusion Criteria

Each patient must meet the following criteria to be eligible for 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 -6 (Visit S1);
3. Fasting calculated LDL-C between 130-189 mg/dL at Week -1 (Visit S2) following washout of all LDL-C-lowering drugs and nutritional supplements;

   Note: LDL-C may be repeated 1 time with the screening period extended up to 1 week. 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.
4. Patient is sufficiently stable and suitable to undergo washout of all LDL-C-lowering drugs and nutritional supplements for 12 weeks (with potential for 1 week extension) based on Investigator assessment;
5. Men and nonpregnant, nonlactating women. Women must be one of the following:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      i. ≥55 years, or
      ii. <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation, or
   c. Women of childbearing potential willing to use one acceptable method of birth control during the study and for 30 days after the end of treatment including:
      i. birth control medications,
      ii. placement of an intrauterine device with or without hormones,
      iii. barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly,
      iv. vasectomized male partner who is the sole partner for this patient,
      v. 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.

7.2. Subject Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate:

1. Body mass index (BMI) >50 kg/m^2;
2. History of documented clinically significant cardiovascular disease including, but not limited to:
   a. Myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary artery bypass graft, stroke, transient ischemic attack, cerebrovascular event, symptomatic carotid artery disease, or symptomatic peripheral arterial disease,
   b. Uncontrolled hypertension, defined as sitting mean systolic blood pressure (SBP) ≥160 mm Hg and/or diastolic blood pressure (DBP) ≥100 mm Hg after sitting quietly for 5 minutes.

      Note: At the discretion of the investigator, a single repeat sitting mean SBP and DBP may be completed at a separate visit. For those patients who have repeat sitting mean SBP and DBP assessment, the repeat values will be used to determine eligibility.
   c. An arrhythmia requiring medical intervention,
   d. Abdominal aortic aneurysm,
   e. New York Heart Association (NYHA) Class III and IV heart failure;
3. Fasting TG >400 mg/dL at Week -1 (S2);

   Note: TG may be repeated 1 time with the screening period extended up to 1 week. For those patients who have a repeat TG, the repeat value will be used to determine eligibility.
4. History of type 1 or type 2 diabetes or fasting glucose >125 mg/dL at Week -6 (Visit S1);
5. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -6 (Visit S1);
6. Liver disease or dysfunction, including:
   a. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Week -1 (Visit S2), or
   b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥2 × ULN at Week -6 (Visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease or if the patient has a history of Gilbert's Disease, the patient may be enrolled in the study.

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

7. Renal dysfunction or glomerulonephritis, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min at Week -6 (Visit S1);

   Note: At the discretion of the investigator, a single repeat of eGFR may be completed. For those patients who have a repeat eGFR, the repeat value will be used to determine eligibility;

8. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption;
9. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL at Week -6 (Visit S1);
10. 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;
11. Unexplained creatine kinase (CK) >3 × ULN at any time prior to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization;
12. History of drug or alcohol abuse within the last 2 years or reported current consumption of >14 alcoholic drinks/week, or any illicit drug use, history of amphetamine and derivatives abuse or cocaine abuse. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator;
13. Blood donation, participation in a multiple blood draws, clinical study, major trauma, blood transfusion or surgery with or without blood loss within 30 days prior to randomization;
14. Use of any experimental or investigational drugs within 30 days prior to screening;
15. Previous enrollment in a bempedoic acid clinical study;
16. Use of these prohibited drugs and/or nutritional supplements prior to randomization or planned use during the study:
    a. LDL-C lowering drugs and/or nutritional supplements (within 5 weeks prior to randomization),
    b. Probenecid or cyclosporine (within 2 weeks prior to randomization),
    c. Potent CYP3A4 inhibitors including amiodarone, azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), bosentan, clarithromycin, cobicistat, conivaptan, danazol, daptomycin, diltiazem, domperidone, erlotinib, erythromycin, fusidic acid, mibefradil, nefazodone, piperaquine, protease inhibitors (atazanavir, boceprevir, darunavir, delavirdine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir), quinupristin/dalfopristin, telithromycin, verapamil (within 2 weeks prior to randomization),

d. Systemic corticosteroids (topical corticosteroids are allowed; within 5 weeks prior to randomization);

17. Planned initiation or dosing changes of these allowed drugs prior to or during the study:
    a. Hormone replacement (within 5 weeks prior to randomization),
    b. Thyroid replacement (within 5 weeks prior to randomization),
    c. Obesity medication (within 3 months prior to randomization);
18. 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;
19. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or any Sponsor personnel.

7.3. Patient Lifestyle and Dietary Guidelines

Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples (water and concomitant medications, but not IMP are permitted).

Beginning at screening, patients will be counseled to follow a heart healthy diet as per local or regional guidelines and should be encouraged (as able) to participate in a stable, regular exercise program throughout the study.

8. TREATMENT OF PATIENTS

8.1. Administration of Investigational Medicinal Product

During the Treatment Period, patients will be randomized to receive IMP of either bempedoic acid 180 mg + ezetimibe 10 mg + atorvastatin 20 mg or placebo once daily. Each daily allotment of IMP is comprised of one bempedoic acid tablet, one overencapsulated ezetimibe tablet and one overencapsulated atorvastatin tablet provided in a blister package. The placebo blister pack will contain the corresponding matching placebo of the three drugs. Patients will be instructed to ingest IMP orally once daily with or without food. On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed.

If the patient forgets to take IMP 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 morning. Details describing the reasons for missed doses should be documented in the patient's medical records and electronic case report form (eCRF). Extra IMP is provided and can be used, if needed, prior to the next visit or to replace an allotment of IMP that cannot be used because it is lost or damaged.

Other details regarding IMP, including description, supply and control, accountability, handling, and disposal are provided in Section 9.

8.2. Prior and 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 case report form (CRF) will be used to record medications, herbal remedies, vitamins, other nutritional supplements, and over-the-counter medications taken within 6 weeks prior to screening and during the study.

8.2.1. Prohibited Medications and Dietary Supplement

Patients will be required to stop taking all prescription or nonprescription drugs or nutritional supplements taken for the purpose of lipid regulation at least 5 weeks prior to randomization (approximately Study Day -35). Use of any drug(s) listed below either in mono or combination therapy are prohibited during the study:

Statins (within 5 weeks prior to randomization):

- Atorvastatin (Lipitor®) (other than sponsor provided)
- Fluvastatin (Lescol®)
- Lovastatin (Mevacor®, Altoprev™)
- Pravastatin (Pravachol®)
- Rosuvastatin Calcium (Crestor®)

- Simvastatin (Zocor®)
- Pitavastatin (Livalo®)

Selective cholesterol and/or bile acid absorption inhibitors (within 5 weeks prior to randomization):

- Ezetimibe (Zetia®, Ezetrol®)
- Cholestyramine (Questran®, Questran® Light, Prevalite®, Locholest®, Locholest® Light)
- Colestipol (Colestid®)
- Colesevelam HCl (WelChol®, Cholestagel®)

Fibrates (within 5 weeks prior to randomization):

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

PCSK9 inhibitors (within 5 weeks prior to randomization):

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

Other Lipid Regulating Drugs (within 5 weeks prior to randomization):

- Niacin (Niaspan® Rx and OTC)
- Omega-3-acid Ethyl Esters (Lovaza® and OTC fish oil)
- Statin fixed dose combinations (eg, Atozet®, Vytorin®, Inegy®)

Lipid Altering Nutritional Supplements (within 5 weeks prior to randomization):

- Berberine
- Psyllium (Metamucil®)
- Green tea extract
- Niacin (crystalline >500 mg/day or slow release or timed release at any dose)
- Sitostanol (found in oral nutritional supplements and some margarines, such as Benecol)
- Beta-sitosterol (found in oral nutritional supplements and some margarines, such as Promise Activ)
- Cholestin (red yeast rice, also known as monascus purpureus extract)

- Pantothine
- Policosanol

Other Drugs:

- Probenecid or cyclosporine (within 2 weeks prior to randomization)
- Potent CYP3A4 inhibitors including amiodarone, azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), bosentan, clarithromycin, cobicistat, conivaptan, danazol, daptomycin, diltiazem, domperidone, erlotinib, erythromycin, fusidic acid, mibefradil, nefazodone, piperaquine, protease inhibitors (atazanavir, boceprevir, darunavir, delavirdine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir), quinupristin/dalfopristin, telithromycin, verapamil (within 2 weeks prior to randomization)
- Systemic corticosteroids (topical corticosteroids are allowed (within 5 weeks prior to randomization)

8.2.2. Permitted Medications

Permitted medications must be stable for at least 2 weeks prior to Visit S1 (Week -6) with the exception of the following:

- Hormone replacement (within 5 weeks prior to randomization)
- Thyroid replacement (within 5 weeks prior to randomization)
- Obesity medication (within 3 months prior to randomization)

8.3. Treatment Assignment, Randomization, and Blinding

During the Treatment Period, patients will receive double-blind IMP. At Day 1 (Visit T1), patients will be randomized to receive either bempedoic acid 180 mg/day + ezetimibe 10 mg + atorvastatin 20 mg or placebo. The investigator or designee will utilize Interactive web response system (IWRS) during the visit to obtain a randomization number and the appropriate IMP container via medication identification numbers (MED ID). A patient is considered to be randomized when they have been assigned a randomization number by IWRS.

The randomization number will be determined by a computer-generated random code and will correspond to a treatment group according to patient's sequential entrance into the study. The randomization schedule for blinding of treatment assignment will be generated by the contract research organization (CRO), provided to IWRS, and released only after the study is complete and the database is locked.

During the Treatment Period, Sponsor, site personnel, CRO, and patient will all be unaware of patient's treatment assignment.

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.

Post-randomization values for individual laboratory measures for LDL-C, non-HDL-C, TC, TG and HDL-C that may inadvertently suggest treatment assignment will not be available to personnel from the clinical site, the patient, the Sponsor, or the CRO. While knowledge of these values does not truly 'unblind,' the collection of these lab assessments by the investigator, all collaborating physicians, or the patients locally (outside the study visits) is strongly discouraged. Investigators should not perform testing of these analytes at the local lab during the conduct of the study.

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Description of Investigational Medicinal Product

Table 2: Investigational Medicinal Products

Product Name:	**Investigational Medicinal Product**	
	Bempedoic acid	**Placebo to Match Bempedoic Acid**
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure:	9 count blister card with child resistant closures	9 count blister card with child resistant closures
Route of Administration:	Oral, daily at approximately the same time, with or without food	Oral, daily at approximately the same time, with or without food
Physical Description:	[redacted]	
Manufacturer (Fill/Finish):		
Product Name:	**Investigational Medicinal Product**	
	Ezetimibe	**Placebo to Match Ezetimibe**
Dosage Form:	Overencapsulated tablets	Capsules
Unit Dose:	10 mg	Not applicable
Container/Closure:	9-count blister card with child-resistant closures	9-count blister card with child-resistant closures
Route of Administration:	Oral, daily at approximately the same time, with or without food	Oral, daily at approximately the same time, with or without food
Physical Description:	TBD	TBD
Manufacturer (Fill/Finish):	TBD	[redacted]
Product Name:	**Investigational Medicinal Product**	
	Atorvastatin	**Placebo to Match Atorvastatin**
Dosage Form:	Overencapsulated tablets	Capsules
Unit Dose:	20 mg	Not applicable
Container/Closure:	9-count blister card with child-resistant closures	9-count blister card with child-resistant closures
Route of Administration:	Oral, daily at approximately the same time, with or without food	Oral, daily at approximately the same time, with or without food
Physical Description:	TBD	TBD
Manufacturer (Fill/Finish):	TBD	[redacted]

Please see Pharmacy Manual for detailed storage requirements and instructions.

9.2. Investigational Medicinal Product Supply and Control

The Sponsor will supply the IMP for this study as described above. 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 IMP packaging) will be obtained via IWRS and used to select double-blind IMP from available clinical supplies at the clinical site.

IMP will be dispensed by the investigator or other qualified site personnel only to appropriate patients who have provided written informed consent.

9.3. Packaging and Labeling

Double-blind IMP will be packaged in blister pack. Each blister pack will contain a 9-day supply and 3 blister packs will be provided in drug kit.

The IMP labels will include protocol number, MED ID number, patient identification number, lot number, site number and investigator name in addition to standard language regarding warnings and regulations, administration and storage of the product.

9.4. Investigational Medicinal Product Adherence

At each clinic visit during the Treatment Period, designated clinical site staff will assess patient IMP intake adherence by counting the number of doses that are returned as unused and by querying the patient with regards to daily intake. If the patient has not taken multiple doses 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 during the Treatment Period will continue to be counseled on the importance of carefully following all dosing instructions, but will not be removed from the study.

9.5. Investigational Medicinal Product Accountability

Patients will be instructed to return all packaging and unused IMP at every visit for assessment of adherence and drug 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 adherence, and relevant documentation of discrepancies
- Nonstudy disposition (eg, lost, broken, wasted)
- Amount returned to Sponsor (or designee)/destroyed or amount destroyed per local standard operating procedure (SOP) following accountability by site monitor.

9.6. Investigational Medicinal Product Handling, Storage, and Disposal

The Principal Investigator will ensure that all IMP is stored in a secured area, under recommended storage conditions [redacted] in accordance with applicable regulatory requirements for investigational drugs. Access to IMP will be limited to those clinical site personnel authorized by the investigator. Upon completion or termination of the study, all IMP and used and unused 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 AND SCHEDULE OF ASSESSMENTS

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). It is the investigator's responsibility that no study-related procedure will be performed until the patient has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an ICD approved by the Sponsor (or designee) and the Institutional Review Board (IRB). The written ICD should be prepared in the local language(s) of the potential patient population.

10.2. Interactive Web Response System and eCRFs

Data will be captured on eCRFs. Randomization, IMP (re)ordering, IMP distribution, and patient status tracking will occur via IWRS. Instructions for these systems and additional contact time points for IWRS will be provided separately.

10.3. Patient Identification Numbers

A unique patient identification number will be assigned to each patient to identify each patient throughout the study. Patient identification numbers will be assigned sequentially by IWRS at the time of informed consent during the screening module transaction and is comprised of protocol, site, and patient-specific numbers.

10.4. Rescreening

Patients who are screening failures due to stability requirements for a condition or concurrent medication or other reason may be considered for rescreening after consultation with the Sponsor (or designee). If rescreened, these patients must also be re-consented and screening procedures must be repeated. If a patient is a screen failure, or if a patient discontinues from the study, their patient ID number will not be assigned to another patient.

10.5. Procedures and Schedule of Assessments

The study is comprised of 2 distinct periods: screening 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.

10.5.1. Screening Week -6 (Visit S1; Day -42 to Day -37)

The screening period will begin with a screening visit that will occur 6 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:

- Assess AEs and serious adverse events (SAEs) (starting from signing the informed consent document)

- Demographics
- Clinically relevant medical history
- Prior and concomitant medication review
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Height (cm), and weight (kg)
- Vital signs
- Central clinical laboratory evaluations:
  - Thyroid-stimulating hormone (TSH)
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - Serum pregnancy test (in female patients of childbearing potential) or follicle-stimulating hormone (FSH) (on postmenopausal women <55 years of age)
- Dietary and lifestyle counselling
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed following review of the Visit S1 central clinical laboratory results (available several days after Visit S1) will be instructed to washout of all lipid-regulating drugs and nutritional supplements 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).

10.5.2. Screening Week -1 (Visit S2; Day -10 to -7)

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

- Concomitant medication review (ongoing)
- Assess AEs and SAEs
- Central clinical laboratory evaluations:
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - Serology (including hepatitis B surface antigen [HBsAg], hepatitis C virus [HCV] antibody)
- Dietary and lifestyle counselling

Note:

- The screening period can be extended by an additional week and an additional visit may be completed prior to Visit T1 if patient fails to meet LDL-C and/or TG entry criterion. If this optional visit is completed, the mean of values from Visit S2 and the additional visit will be used to determine eligibility.

- An additional visit and/or assessment between Visit S1 and Visit T1 MAY be completed if the patient fails to meet diastolic blood pressure (DBP), systolic blood pressure (SBP), TSH, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serology and/or creatine kinase (CK) entry criteria. Patients may qualify for randomization after any associated medications have been adjusted and stabilized and the repeat assessment meets entry criteria.

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

Prior to scheduling Visit T1, screening results will be reviewed to determine whether the patient continues to meet eligibility criteria. At Visit T1, a physical exam and urine pregnancy test will also be completed prior to randomization. Patients not meeting all entry criteria at any point prior to randomization will be screen failures.

If the patient has met all inclusion criteria and none of the exclusion criteria, the patient may be randomized into the double-blind Treatment Period.

Patients 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 Day 1 (Visit T1):

- Concomitant medication review (ongoing)
- Assess AEs and SAEs
- PE
- Review inclusion/exclusion criteria to establish patient eligibility
- Weight
- Vital signs
- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - ApoB and hs-CRP
- Urine pregnancy test (in female patients of childbearing potential)
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind IMP
- Dispense double-blind IMP and provide dosing and storage instructions
- Dietary and lifestyle counselling

10.5.4. Treatment Week 3 (Visit T2; Day 22 ± 3 days)

Patients will undergo the following assessments and procedures at Week 3 (Visit T2):

- Concomitant medication review (ongoing)
- Assess AEs and SAEs
- Weight
- Vital signs
- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL C, HDL C, non-HDL C, and TG)
- Return of IMP; assessment and recording of IMP dosing adherence
- IWRS contact to obtain new MED ID number for double-blind IMP
- Dispense double-blind IMP and provide dosing and storage instruction
- Dietary and lifestyle counselling

10.5.5. Treatment Week 6 (Visit T3; Day 43 ± 3 days)/End of Study or Early Termination

Patients will undergo the following assessments and procedures at Week 6 and/or End of Study/Early Termination:

- Concomitant medication review (ongoing)
- Assess AEs and SAEs
- PE
- Weight
- Vital signs
- Central clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, HDL-C, non-HDL-C, and TG)
  - ApoB and hs-CRP
- Return of IMP; assessment and recording of IMP adherence

10.6. Patient Withdrawal From the Study

Patients must remain in the study until the last scheduled visit at Study Day 43 (Visit T3) to be considered as having completed participation in the study.

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:

- AE
- Patient's withdrawal of consent
- Failure to comply with the protocol
- Lost to follow-up
- Illness, condition, or procedural complication 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.

11. ASSESSMENT OF EFFICACY

11.3 Assessments of Lipids and hs-CRP

Central clinical laboratory samples will be collected and analyzed for the parameters detailed in Table 3. LDL-C will be calculated or measured directly if TG are >400 mg/dL or LDL-C is <50 mg/dL.

Blood draws for lipids (not safety) 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 and concomitant medications [but not IMP] is allowed)
- Blood samples will be drawn only if patient ingested IMP the previous day

Patients are to be in a seated position during the blood collection. Collection schedule and instructions are provided in the Central 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 12.1.5.

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

Table 3: Central Clinical Laboratory Parameters (Lipids and hs-CRP)

Clinical Laboratory Test	Clinical Laboratory Test
Basic Lipid Parameters • Total cholesterol (TC) • Calculated 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) • Apolipoprotein B (ApoB)

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

At all clinic visits, investigators will review all safety information including vital signs, AEs, SAEs, and concomitant medications and will ensure that the collected data are recorded into the appropriate eCRF. Additionally, central 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.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor or its designee if appropriate.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator is responsible for following AEs that are serious or that caused the patient to discontinue before completing the study until the event is resolved or stable. Frequency of follow-up evaluation is left to the discretion of the investigator.

12.1.1. 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.

12.1.2. Vital Signs

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

Vitals will be collected prior to blood collection. Blood pressure (BP) and heart rate will be measured using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper arm. If a fully automated machine is not available, BP may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study. The patient should be in a seated position with feet touching the floor. Patients should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on the ground, and their arms bared and supported at heart level. At each clinic visit, 2 BP measurements will be collected at 1- to 2-minute intervals.

12.1.3. Weight and Height

Body weight will be measured on a calibrated scale in the morning while fasted and after voiding.

Height will be measured using standard clinic procedures.

Body mass index (BMI) will be calculated systematically using the formula:

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

12.1.4. Physical Examination

Physical examinations 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 IMP 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.

12.1.5. Central Clinical Laboratory Tests

12.1.5.1. Central Clinical 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 4. Collection schedule, schedule of laboratory parameters by visit, and instructions are in the Clinical Laboratory Manual provided by Central Laboratory.

Table 4: Central Clinical Laboratory Parameters (Safety)

<table>
<tr><th>Clinical Laboratory Test</th><th>Clinical Laboratory Test</th></tr>
<tr><td>• 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 values only)</td><td rowspan="2">Blood Chemistry (serum, fasting)
• Albumin (Alb)
• Alkaline phosphatase (Alk-P)
• Alanine aminotransferase (ALT; SGPT)
• Aspartate aminotransferase (AST; SGOT)
• Blood urea nitrogen (BUN)
• Calcium (Ca)
• Carbon dioxide (CO_2)
• Chloride (Cl)
• Creatinine
• Creatine kinase (CK)
• Glucose
• Lactate dehydrogenase (LDH)
• Phosphorus
• Potassium (K)
• Sodium (Na)
• Total and direct bilirubin (TB)
• Total protein
• Uric acid</td></tr>
<tr><td>Urinalysis (Dipstick)
• Clarity
• Bilirubin
• Color
• Glucose
• Ketones
• Leukocyte esterase
• Nitrate
• Occult blood
• pH
• Protein
• Specific gravity
• Urobilinogen</td></tr>
<tr><td>Urinalysis (Microscopic) – only if urine dipstick abnormal
• Bacteria
• Casts
• Crystals
• Epithelial cells
• Red blood cells (RBC)
• White blood cells (WBC)</td><td>Coagulation – ONLY in patients receiving anticoagulant therapy measured only at Visit T1 and 3 to 5 days post Visit T1
• Prothrombin time (PT)
• International normalized ratio (INR)</td></tr>
</table>

Table 4: Central Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), optional reflexive Hepatitis C RNA only if HCV is positive • Serum and urine pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; only for postmenopausal females <55 years old) • Thyroid-stimulating hormone (TSH)	

12.1.5.2. Sample Collection, Storage, and Shipping

Central 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. Samples will be processed by the Central Laboratory.

12.1.5.3. 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 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 double-blind IMP. 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 a 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.

12.1.5.3.1. 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; 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 antihepatitis A virus (total), HBsAg (confirmation of screening measurement),

HCV (confirmation of screening measurement), and anti-cytomegalovirus/immunoglobulin M. Epstein-Barr, 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. Although samples will be collected, some repeat LFT parameters may not be measured until elevation is confirmed.

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN but ≤5 × ULN, consideration should be given to administering no further doses of IMP. At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >5 × ULN and no alternative reason for elevation is identified, patient should discontinue IMP. At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following and no alternative reason for elevation is identified, patient should discontinued IMP and be given no further IMP treatment:
  - TB >2 × ULN
  - 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

12.1.5.3.2. 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. If initial CK elevation is >10 × ULN, patients will be instructed to discontinue IMP immediately (instead of continuing IMP until repeat lab value is assessed). It is very important that repeat confirmatory assessment occur as soon as possible (within a day of stopping IMP).

Repeat CK assessment will include query for the nature, duration and intensity of any muscle symptoms; review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology), concomitant medications, and/or other conditions which can cause myopathy; physical examination for muscle tenderness, weakness, and rash; measure serum creatinine, dipstick urinalysis ± microscopy if indicated; and basic metabolic panel.

- 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 IMP with continued CK assessments every 1-2 weeks.

- 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 discontinue IMP:
  - >5 × ULN that is associated with symptoms of muscle pain, muscle weakness, or dark urine; or
  - >10 × ULN, even in the absence of symptoms.
- At the investigator's discretion, IMP may be interrupted and the patient rechallenged with IMP after CK has returned to the baseline level.

12.1.5.3.3. Monitoring and Management of Elevated LDL-C

Post-randomization, LDL-C results will be masked to investigators in order to maintain the blind. The central laboratory will notify the investigator if the patient's LDL-C level is ≥220 mg/dL. The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria. The patients will be counseled on healthy dietary guidelines and reminded to take IMP. If confirmed, the patient will discontinue IMP.

12.1.5.3.4. Monitoring and Management of Elevated TG

Post-randomization, TG results will be masked to investigators in order to maintain the blind. The central laboratory will notify the investigator if patient's TG level is >1000 mg/dL. The patients will be counseled on healthy dietary guidelines and reminded to take IMP. The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the TG value meets the threshold criteria. If confirmed, the patient will discontinue IMP.

12.1.5.3.5. Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

Patients will be educated on the signs and symptoms of hypoglycemia. If such signs and symptoms are experienced, patients will be advised to report them to the study site (see Section 13.3 for additional details).

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 (see Section 13.3 for additional details). This event should be captured as an AE.

12.1.5.4. Total Blood Volume of Central Clinical Laboratory Samples

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

13. ADVERSE AND SERIOUS ADVERSE EVENTS

13.1. Adverse Events

13.1.1. Definition of Adverse Events

An AE is defined as 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. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the patient are recorded in the patient's medical record.

An AE can be:

- Any unfavorable and unintended sign/symptom including an abnormal laboratory finding 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
- Laboratory abnormality or diagnostic test abnormalities (eg, electrocardiogram [ECG] or X-ray) should be reported as an AE if one of the following occurs:
  - Treatment required due to the abnormality
  - Discontinuation of IMP
  - Per Investigator judgement
- TEAEs are defined as AEs that begin or worsen after the first dose of IMP administration as defined in the statistical analysis plan (SAP)

13.1.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction (ADR). "Responses" to a medicinal product means that a causal relationship between the 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).

13.1.3. Reporting for Adverse Events

All AEs occurring during the course of the study (starting from signing informed consent through 30 days after study completion/discontinuation) will be collected on the AE eCRF. Patients should be instructed to report any AE that they experience to the investigator. Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure 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 worsens in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment.

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

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 IMP. 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 IMP.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever, elevated white blood cells [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 IMP administration should be determined by the investigator or study physician after thorough consideration of all facts that are available.

13.1.4. 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.

13.1.5. Relationship

It is the investigator's responsibility to assess the relationship between the IMP and the AE. The degree of "relatedness" of the AE to the IMP 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.
- Possible: Temporal association, but other etiologies are likely the cause. However, involvement of the IMP cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the IMP is discontinued.
- Definite: Established temporal association with administration of the IMP with no other more probable cause. Typically, the event should resolve when the IMP is discontinued and recur on re-challenge.

13.1.6. 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 or stabilization of the event(s).

Patients with AEs related to IMP that are ongoing at study discontinuation or completion must be followed until resolution or for 30 days after study completion, whichever comes first, with the exception of patients reporting SAEs (see Section 13.2.2).

13.1.7. Treatment-Emergent Adverse Events

TEAE are defined as AEs that begin or worsen after the first dose of IMP administration as defined in the SAP.

13.2. Serious Adverse Events

13.2.1. 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: An emergency room visit without hospital admission does not meet inpatient hospitalization criterion, nor does hospitalization for an elective or outpatient procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.2.2. Reporting Serious Adverse Events

All SAEs occurring from the time of informed consent until 30 days following study completion/discontinuation must be reported by the Principal Investigator or designee to the designated Safety contact within 24 hours knowledge of the event. All SAEs that the investigator considers related to IMP that occur after the 30-day follow-up period of the study period must be reported to the Sponsor.

To report the SAE, the SAE form in electronic data capture (EDC) should be completed within 24 hours of becoming aware of the event. If you have questions, please call the designated Safety contact for assistance.

Detailed instructions and contact information for the Safety designee will be provided in the SAE Completion Guidelines.

The investigator is required to submit SAE reports to their IRB 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 IMP 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 designated Safety contact.

The Sponsor (and/or legally transferred designee) will report SAEs and suspected and unexpected serious adverse reactions (SUSARs) as required by global regulatory authorities, IRBs, and/or investigators/institutions in compliance with all reporting requirements according to local regulations, laws, and Good Clinical Practices (GCPs). The investigator should notify their IRB of SAEs occurring at their site and other SAE reports received from the Sponsor, in accordance with local procedures and statutes.

13.2.3. Reporting of Patient Death

The death of any patient during the study or within 30 days after study discontinuation or completion must be reported as an SAE.

13.2.4. Reports of Pregnancy and Lactation

Although not considered an SAE (unless an event occurs with a serious outcome), pregnancy will be collected by the designated Safety contact. If a female patient should become pregnant during the course of the study, the Principal Investigator or designee must contact the designated Safety contact within 24 hours of knowledge of the pregnancy. In addition, a Pregnancy report form must be completed and submitted to the Safety contact.

Patients who become pregnant must discontinue study medication immediately and will continue to be followed until the pregnancy is completed. Once the outcome of the pregnancy is known, the Pregnancy Outcome report form must be completed and submitted to the Safety contact. Patients who lactate during the study may be required to discontinue study medication.

13.3. Adverse Events of Special Interest

Muscle: Muscle events have been associated with statins (Thompson 2003) and other lipid-lowering therapies and are mentioned in the product information for these therapies. Muscle symptoms through AE review, CK elevations, and symptoms of potential myopathy will be closely monitored.

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 × ULN.

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). Summarization of events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms outlined in the SAP.

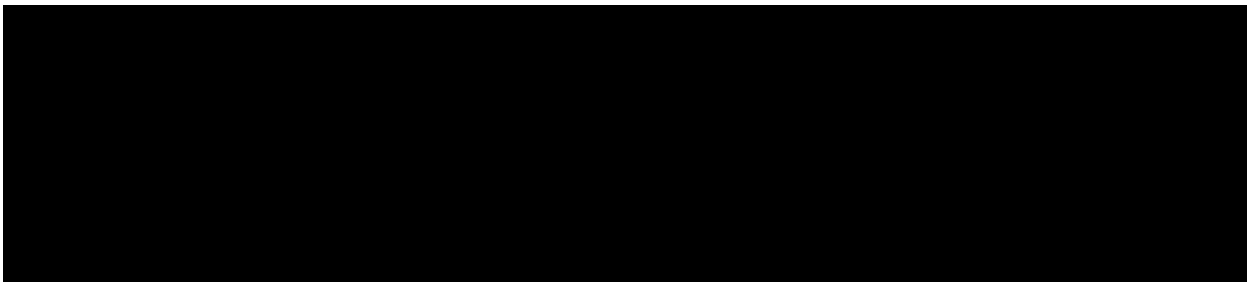
14. STATISTICS

14.1. General Considerations

The statistical analyses described in this section will be performed as further outlined in the SAP, which will be finalized prior to the end of the study. The SAP will supersede the protocol if there are any differences between the 2 documents in the plans for data analysis. The SAP will be included as an appendix in the clinical study report for this protocol.

In general, summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, first and third quartiles, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

14.2. Determination of Sample Size



14.3. Analysis Populations

The modified Intent-to-Treat (mITT) population, used for all of the efficacy analyses, is defined as all randomized patients who received at least 1 dose of IMP and have a baseline assessment and at least 1 postbaseline assessment, excluding any assessment taken more than 2 days after a dose of IMP.

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.

14.4. Disposition, Demographics, and Baseline Characteristics

Disposition, including reason for withdrawal from the IMP and 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.

14.5. Primary Endpoint Analysis

The primary efficacy endpoint is the percent change from baseline to Week 6 in LDL-C. Baseline is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1). An analysis of covariance (ANCOVA) with treatment group as factor and baseline LDL-C as covariate will be performed to compare triplet therapy versus placebo for the primary endpoint using the mITT population (Section 14.3). Missing values at Week 6 will be imputed using the last observation carried forward (LOCF) procedure (only postbaseline

values will be carried forward). 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.

14.6. Secondary Efficacy Endpoint Analyses

Secondary efficacy endpoints, which include the percent change from baseline to Week 6 in additional lipid and cardiometabolic biomarkers, will be analyzed in a similar manner as the primary efficacy endpoint. Baseline for non-HDL C, HDL-C, TC, and TG is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1), while baseline for ApoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value.

Statistical testing of primary and secondary efficacy endpoints will be 2-sided and conducted at the 5% level of significance with no adjustment for multiple comparisons.

14.7. Safety Endpoints

Descriptive summary will be provided for safety endpoints.

The MedDRA will be used to code all AE to a system organ class (SOC) and a preferred term.

The summarization of AEs will include only TEAEs defined as AEs that begin or worsen after first dose of IMP administration as defined in the SAP. All TEAEs, SAEs, AEs leading to withdrawal of IMP, fatal AEs and AEs of special interest will be summarized by SOC and preferred term in descending order of frequency by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, glucose, and urinalysis; PE findings; vital signs; and weight will be summarized by the value and by change or percent change from baseline in the value (where appropriate) at each postbaseline time point.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Conference on Harmonisation (ICH) and GCP guidelines, national 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, IMP dispensing log, pharmacy records, patient sign-in sheets, patient-completed questionnaires, and telephone logs) required to confirm information contained in the eCRFs.

A monitoring visit should include a review of the essential clinical study documents (regulatory documents, CRFs, 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. These documents should be redacted by the site in accordance with local law.

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.

15.2. 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 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.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor (or designee) may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Institutional Review Board 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. For locations participating within the US, the IRB must comply with the provisions specified in 21 Code of Federal Regulations (CFR) Part 56 and GCP guidelines, and applicable pertinent state and federal requirements.

IRBs 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 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 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 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. This includes notification to the IRB 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, and submission of final study reports and summaries to the IRB.

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

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

17.2. 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 GCP, applicable regulatory requirements, and policies and procedures as outlined by the ethical requirements for IRB 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. 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).

17.3. 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 clearly understand 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 on the Sponsor agreed ICD. Updates to the ICD during the conduct of the study will be communicated by written letter from the Sponsor to the investigator. The ICD should be provided in the appropriate language of the patient population.

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

17.4. Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained.

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 designee). 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 designee). 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 local regulations will be adhered to and detailed appropriately in the ICD.

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

Applicable regulations require the Sponsor (or designee) 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 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.

18.2. 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, IMP 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.

18.3. 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 correspondence, clinical study materials and supplies shipment manifests,

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

Source documentation is defined as any hand-written or computer-generated document that contains medical information or test results that have been collected for or in support of the protocol specifications (eg, laboratory reports, clinic notes, IMP disposition log, pharmacy records, patient sign-in sheets, 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 IMP 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 IMP, 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 48 hours following the evaluation.

19. ADMINISTRATIVE CONSIDERATIONS

19.1. Investigators

The investigator must agree to the responsibilities and obligations listed below, as specified by the appropriate FDA 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 IMP are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB 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 IMP
- 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 will be responsible for the initial and continuing review and approval of the clinical investigation
- Agree to promptly report to the IRB 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 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
  - Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf

19.2. Study Administrative Structure

Central Laboratory:

[redacted]

Randomization, IWRS, Medical Writing:

TBD

Statistical Analysis, Study Management and Monitoring, Data Management, Programming:

[redacted]

Medical and Safety Services including Medical Monitoring:

[redacted]
Cell phone #: [redacted]
Email: [redacted]

[redacted]
Office phone #: [redacted]
Cell phone #: [redacted]
Email: [redacted]

19.3. Amendments and Study Termination

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 approval. Documentation of amendment approval by the investigator and IRB 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 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.

The Sponsor reserves the right to terminate this study at any time.

19.4. 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 IMP such that his or her research might be biased by such incentive.

20. 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, European Medicines Agency, 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 individual investigators. 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.

21. LIST OF REFERENCES

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

22. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS

Schedule of Events					
Visit	**S1**	**S2[1]**	**T1**	**T2**	**T4**
Week	**-6**	**-1**	**0**	**3**	**6/EOS/ET[2]**
Procedure	**Day -42 to -37**	**Day -10 to -7**	**Day 1**	**Day 22 ± 3**	**Day 43 ± 3**
Informed Consent	X				
Enrollment Criteria	X	X	X		
Demographics	X				
Medical History	X				
Concomitant\Prohibited Medications	X	X	X	X	X
Adverse Event Recording		X	X	X	X
Physical Exam			X		X
Weight[3]	X		X		X
Height/BMI	X				
Vital Signs[4]	X	X	X	X	X
Serology[5]		X			
Serum Pregnancy/FSH[6]	X				
Urine Pregnancy[6]			X		
TSH	X				
Clinical Safety Labs[7]	X		X	X	X
Basic Fasting Lipids[8]	X	X	X	X	X
Special Fasting Lipids and Other Biomarkers[9]			X		X
Dietary and Lifestyle Counselling	X	X	X	X	
Randomization			X		
Double Blind IMP Dispensing			X	X	
IMP Return				X	X

BMI = body mass index; FSH = follicle-stimulating hormone, TSH = thyroid-stimulating hormone, EOS = End of Study, ET = Early Termination.

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

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

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

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

[5] Serology for Hep B antigen, Hep C antibody.

[6] FSH completed in appropriate postmenopausal women only; pregnancy test completed in non-postmenopausal women only.

[7] Clinical safety labs include hematology, blood chemistry, and urinalysis. Coagulation panel ONLY in patients receiving anticoagulants measured only at T1 and repeat 3-5 days after starting IMP.

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

[9] Includes ApoB and hs-CRP

APPENDIX 2. SPONSOR'S SIGNATURES

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Triplet Therapy with Bempedoic Acid (ETC-1002) 180 mg, Ezetimibe 10 mg, and Atorvastatin 20 mg in Patients with Elevated LDL-C

Study Number: 1002-038

Final Date: 11 November 2016

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: 15 Nov 2016

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Triplet Therapy with Bempedoic Acid (ETC-1002) 180 mg, Ezetimibe 10 mg, and Atorvastatin 20 mg in Patients with Elevated LDL-C
Study Number:	1002-038
Final Date:	11 November 2016

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: 11/14/2016

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Triplet Therapy with Bempedoic Acid (ETC-1002) 180 mg, Ezetimibe 10 mg, and Atorvastatin 20 mg in Patients with Elevated LDL-C
Study Number:	1002-038
Final Date:	11 November 2016

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:

[redacted] VP Clinical Development
on behalf of [redacted]

Signed: [redacted] Date: 11/15/2016

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Triplet Therapy with Bempedoic Acid (ETC-1002) 180 mg, Ezetimibe 10 mg, and Atorvastatin 20 mg in Patients with Elevated LDL-C

Study Number: 1002-038

Final Date: 11 November 2016

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: