BEMPEDOIC ACID (ETC-1002)

1002-039

A RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BEMPEDOIC ACID (ETC-1002) 180 MG QD WHEN ADDED TO PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9)-INHIBITOR THERAPY

Study Phase:	2
IND Number:	106,654
EudraCT Number:	n/a
Indication:	Treatment of hyperlipidemia
Investigators:	Approximately 20-30 sites located in North America
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108 Phone: 734-862-4840 Fax: 734-582-9720
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

Version	Date
Original Protocol	22 November 2016
Protocol Amendment 1:	05 March 2017

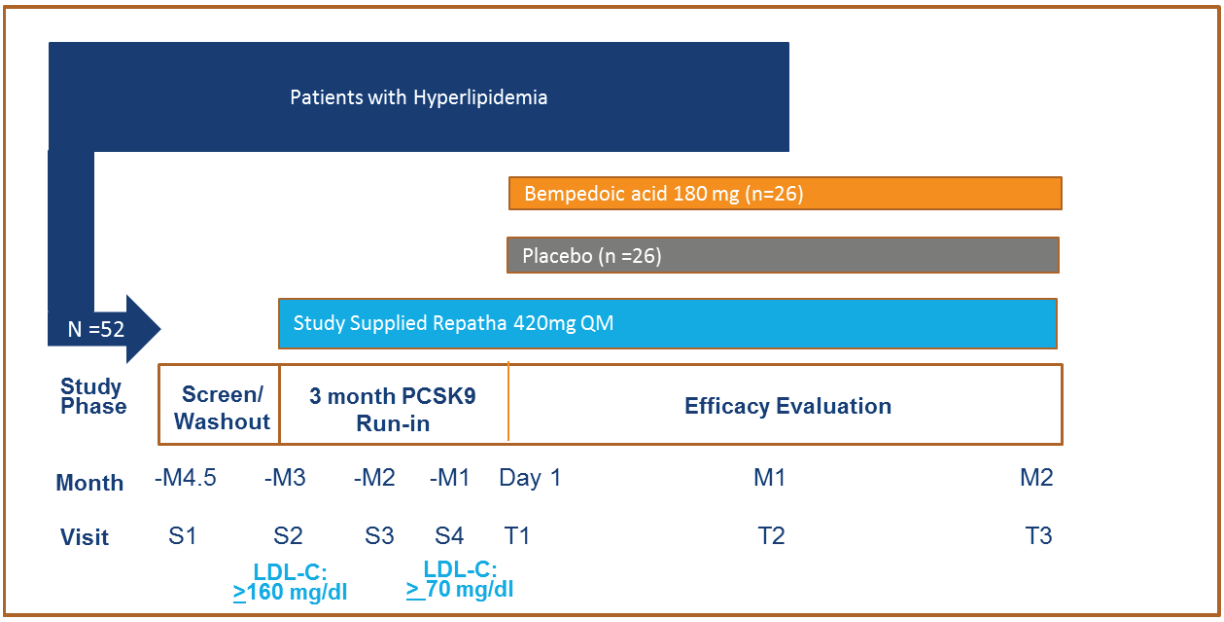
NCT number: NCT03193047
This NCT number has been applied to the document
for purposes of posting on clinicaltrials.gov

2. SYNOPSIS

Name of Sponsor: Esperion Therapeutics, Inc.
Name of Investigational Product: Bempedoic acid (ETC-1002) film-coated tablets
Name of Active Ingredient: Bempedoic acid
Title of Study: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy
Study Number: 1002-039
Phase of Development: 2
Clinical Sites: Approximately 20 sites located in North America
Objectives: **Primary:** • To assess the 2-month efficacy of bempedoic acid 180 mg/day vs placebo in the reduction of low-density lipoprotein cholesterol (LDL-C) in patients on proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) therapy **Secondary:** • To assess the 1-month efficacy of bempedoic acid 180 mg/day vs placebo in the reduction of LDL-C in patients on PCSK9i therapy • To evaluate the effect of bempedoic acid 180 mg/day vs placebo on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and high-sensitivity C-reactive protein (hs-CRP) after 1 and 2 months of treatment • To evaluate the safety and tolerability of bempedoic acid 180 mg/day compared to placebo in patients on PCSK9i therapy **Exploratory:** [redacted]

Methodology:

1002-039 STUDY DESIGN



This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 20 clinical sites in North America. Screening Visit S1 will occur approximately 4.5 months prior to randomization. After providing informed consent at Visit S1, patients will stop all background lipid-lowering therapy and lipid-modifying nutritional supplements, if applicable. All patients will return to the clinic on Month -3 (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate PCSK9 background therapy (Repatha 420 mg once monthly [QM]). Sites that do not use a local lab may need to bring patients back for another visit to administer PCSK9 background therapy, as a qualifying LDL-C value is required prior to initiating the 3-month PCSK9i run-in period. No other background lipid-modifying therapy except study provided PCSK9i will be permitted during the trial. After 1 month (at least 30 ± 3 days), patients will return to the clinic for Month -2 (Visit S3) followed by Month -1 (Visit S4) 30 ± 3 days later. During these visits, Repatha will be administered, labs will be collected, and safety assessed. At Visit S4, LDL-C will be checked a second time prior to randomization. Patients with an LDL-C ≥70 mg/dL (via central lab only) at this visit will qualify for randomization. Patients with LDL-C <70 mg/dL at Visit S4 will be screen failed and no further PCSK9i therapy will be administered. Day 1 should occur 30 days ± 3 days after Visit S4, once LDL-C eligibility is established. On Day 1, qualified patients will be randomized 1:1 to bempedoic acid 180 mg/day (n = 26) or matching placebo (n = 26). Randomized patients will return for clinic visits at Month 1 (Visit T2) and Month 2 (Visit T3). Both study drug and PCSK9i doses will be administered on site during clinic visits after all procedures have been completed.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data across the bempedoic acid program.

Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline to Month 2 in LDL-C.

Secondary Endpoints

1. Percent change from baseline to Month 1 in LDL-C
2. Change from baseline to Month 1 and Month 2 in LDL-C
3. Percent change from baseline to Month 1 and Month 2 in ApoB, non-HDL-C, TC, and hs-CRP
4. Safety and tolerability of bempedoic acid in this patient population over 2 months, as assessed by adverse events (AEs) and clinical laboratory values

Exploratory Endpoints

[redacted]

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

Number of patients (planned): Approximately 52 adult male and female patients

Diagnosis and Criteria for Inclusion:

Key inclusion criteria

1. Provision of written informed consent must be obtained prior to any study-specific procedure.
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Month -4.5 (Visit S1)
3. Fasting, calculated LDL-C at screening (Visit S2) ≥160 mg/dL and ≥70 mg/dL at Visit S4

   Note: A single repeat of LDL-C may be completed. For those patients who have a repeat LDL-C, the average of the 2 values will be used to determine eligibility.
4. Men and nonpregnant, nonlactating women. Women must be:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      - ≥55 years, **or**
      - <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; **or**
   c. Women of childbearing potential willing to use 2 acceptable methods of birth control including:
      - oral, implanted, topical or injectable birth control medications
      - placement of an intrauterine device with or without hormones
      - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
      - vasectomized male partner who is the sole partner for this patient
      - true abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception)

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

Key exclusion criteria

1. Homozygous Familial Hypercholesterolemia (HoFH)
2. Total fasting TG ≥500 mg/dL (5.6 mmol/L at Month -3 (Visit S2).

   Note: A single repeat of TG may be completed. For those patients who have a repeat TG, the average of the 2 values will be used to determine eligibility.
3. Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Month -4.5 (Visit S1).

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the average of the 2 values will be used to determine eligibility.
4. All patients with known cardiovascular disease (CVD) or peripheral arterial disease (PAD) or cerebrovascular disease (CD).
5. History of type 1 or type 2 diabetes or laboratory evidence of diabetes (fasting blood glucose [FBG] >126 mg/dL or glycosylated hemoglobin, Type A_{1C} [HbA_{1C}] >6.5%) without prior diagnosis of diabetes at Month -4.5 (Visit S1)
6. Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg at Month -4.5 (Visit S1).
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Month -4.5 (Visit S1).
8. Liver disease or dysfunction, including:
   a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Month -4.5 (Visit S1).
   b. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Month -4.5 (Visit S1).

      Note: If total bilirubin (TB) ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, the patient may be enrolled in the study.

      Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed. For those patients who have a repeat ALT and/or AST, the average of the 2 values will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but reflexive test for Hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption.
10. History of hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Month -4.5 (Visit S1)
11. History of malignancy (except non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ).
12. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other meds for chronic pain that have been stable, without evidence of abuse prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
14. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood

transfusion, or major surgery with or without blood loss within 30 days prior to randomization

15. Use of any experimental or investigational drugs within 30 days or 5 half-lives, whichever is longer
16. Previous enrollment in a Esperion Phase 3 bempedoic acid (ETC-1002) clinical study
17. Use of a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to screening, such as: anacetrapib, dalcetrapib, or evacetrapib.
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Month -4.5 [Visit S1]),
    - Lomitapide or apheresis therapy (must be stopped at least 3 months prior to Month -4.5 [Visit S1]),
    - Red yeast rice containing products (must be stopped on or before Month -4.5 [Visit S1]),
    - Lipid-regulating drugs or supplements (must be stopped on or before Month -4.5[Visit S1])
19. Planned initiation or changes to the following drugs prior to Month -4.5:
    - Hormone replacement (6 weeks prior to Month -4.5)
    - Thyroid replacement (6 weeks prior to Month -4.5)
    - Obesity medication (3 months prior to Month -4.5)
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study.
21. Patient is pregnant or breast feeding, or planning to become pregnant during treatment and/ or within 30 days after the end of treatment
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
23. Heterozygous familial hypercholesterolemia (HeFH)
24. Concomitant use of a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at (Visit S1) or prior use within the past 16 weeks of Visit S1

Test product, dose, and mode of administration:

- Bempedoic acid 180-mg tablets/once per day
- Matching placebo tablets/once per day
- PCSK9i – Repatha 420 mg injection once monthly

All study drug (bempedoic acid or placebo) will be ingested once daily with or without food. On clinic days patients will come to the clinic in the fasted state and the PCSK9i and study drug will be administered after all study procedures have been conducted. PCSK9i injections must be administered consistently throughout the trial within 30 ± 3 days from the previous dose. Efficacy will vary if the doses are not consistently administered.

Duration of treatment:

The duration of treatment will be composed of a 1.5-month screening period, a 3-month PCSK9i lipid stabilization period, and a 2-month treatment period.

Criteria for evaluation:

Efficacy:

Lipid and Cardiometabolic Assessments:

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

Other biomarker and PK samples:

Pharmacokinetics

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

Safety:

Safety Assessments:

- Adverse events and serious adverse events (SAEs) will be collected and reported. Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, HbA_{1C}, fasting glucose, and urinalysis), physical examination (PE) findings, vital signs, and weight.

Clinical Laboratory Assessments:

- Hematology: Hematocrit (Hct), Hgb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute values only)
- Urinalysis (Dipstick): Clarity, bilirubin, color, glucose, ketones, leukocyte esterase, nitrite, occult blood, pH, protein, specific gravity, urobilinogen
- Urinalysis (Microscopic): Obtain centrally only if positive urine dipstick; bacteria, casts, crystals, epithelial cells, RBC, and WBC
- In patients receiving anticoagulant therapy that in the investigator's judgement require monitoring, PT/international normalized ratio (INR) will be evaluated at Visit T1 and 3 to 5 days post Visit T1 using a local or central lab
- Serum Chemistry (fasting): Albumin (ALB), alkaline phosphatase (ALK-P), ALT (or serum glutamic pyruvic transaminase [SGPT]), AST (or serum glutamic oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO_2), chloride (Cl), creatinine, CK, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid
- HbA_{1C}

Other Screening Laboratories:

- Serum pregnancy test (only for females who are of childbearing potential), TSH, FSH (in females naturally postmenopausal, females <55 years of age at screening)

Safety and Monitoring:

Post-randomization, lipid results will be masked in order to maintain the blind.

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

Adverse Events Associated with Experience with bempedoic acid to date:

Potential AEs:

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

Musculoskeletal Safety:

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

Hepatic:

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

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

Statistical methods:

Sample Size

The planned total sample size for this study is 52 with 26 patients in the bempedoic acid 180 mg group and 26 in the placebo group. This sample size is expected to [redacted]

Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy analyses, is defined as all randomized patients with a baseline lipid value, at least 1 postbaseline lipid value, and having taken their study drug within 2 days of the lipid measurement. The FAS is also known as the modified intention-to-treat (mITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received. Other subsets of the FAS will be considered to evaluate primary and secondary endpoints as sensitivity analyses and the details will be described in the statistical analysis plan (SAP).

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

Primary Endpoint

The primary efficacy endpoint is the percent change from baseline to Month 2 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline LDL-C as a covariate. The details of the ANCOVA model and options to correct for unequal variances will be described in the SAP. Baseline LDL-C is defined as the average of S4 and Day 1 values, if only 1 value is available, then that single value will be used as baseline. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Patients who are missing their Month 2 LDL-C will have their Month 2 value imputed by last observation carried forward (LOCF). The least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

Secondary and Exploratory Efficacy Endpoints

Secondary endpoints based on lipid parameters will be analyzed in the similar fashion as for the primary endpoint.

Safety Analyses

Descriptive summary will be provided for the safety data in this study.

The subject incidence of all treatment-emergent AEs (TEAE), SAEs, related AEs, AEs leading to withdrawal of study drug and/or study, fatal AEs, and AEs of special interest (AESI) will be tabulated by system organ class (SOC) and preferred term in descending order of frequency and by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, HbA_{1C}, 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 postbaseline time point.

Hepatic Safety

For liver-associated enzymes and TB, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. All liver-associated laboratory abnormalities will be assessed for Hy's Law criteria (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN in the absence of other known causes).

Musculoskeletal Safety

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

Diabetes/Hyperglycemia

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

Renal Safety

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

Neurocognitive Events

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

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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
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular diseases
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CD	Cerebrovascular disease
CETP	Cholesterol ester transfer protein
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
C_{max}	Time to peak maximum concentrations
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CRO	Contract research organization
CV	Cardiovascular

Abbreviation or Specialist Term	Explanation
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
ETC-1002	Bempedoic acid
EU	European Union
FAS	Full analysis set
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies
[redacted]	
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HoFH	Homozygous familial hypercholesterolemia
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LOCF	Last observation carried forward
[redacted]	
LPLV	Last patient last visit
LS	Least square
LSM	Least square 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
Na	Sodium
NA	Not applicable
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
PAD	Peripheral arterial disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	PCSK9 inhibitor
PE	Physical examination
PK	Pharmacokinetic(s)
PT	Prothrombin time
QM	Once monthly
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

Abbreviation or Specialist Term	Explanation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SOP	Standard operating procedures
SP	Safety population
SUSARS	Suspected and unexpected serious adverse reactions
$t_{½}$	Terminal elimination half-live
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid-stimulating hormone
TQT	Thorough QT/QTc
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

4. INTRODUCTION

4.1. Overview of the Disease Under Study

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

Proprotein convertase subtilisin kexin type 9 (PCSK9) reduces LDL receptor recycling to the hepatic surface, thereby limiting removal of LDL particles from the circulation. Monoclonal antibodies neutralize PCSK9 and reduce LDL-C levels when administered alone or in combination with other background therapies.

Elevated LDL-C is a major modifiable risk factor for the development of atherosclerosis and atherosclerotic cardiovascular diseases (ASCVD) (Sharrett 2001). Despite aggressive interventional and pharmacologic therapies, CV disease is the number 1 cause of death globally (WHO 2015). An estimated 17.5 million people died from CV diseases in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease (CHD) and 6.7 million were due to stroke (WHO 2015). Cardiovascular disease remains the leading cause of death among Europeans, Americans, and around the world. The Global Burden of Disease study estimated that 29.6% of all deaths worldwide (approximately 15.6 million deaths) were caused by CV disease in 2010, more than all communicable, maternal, neonatal and nutritional disorders combined, and double the number of deaths caused by cancers (Nichols 2014). In the United States (US), based on 2011 death rate data, more than 2150 Americans die from CV diseases daily, an average of 1 death every 40 seconds. Approximately 155,000 Americans dying from CV disease are less than 65 years of age. In 2011, 34% of deaths due to CV disease occurred prior to the age of 75 years, less than the current 78.7-year average life expectancy (Mozffarian 2015). As such new therapies to combat this global public health problem are needed.

Global guidelines recommend lowering of LDL-C to levels below 100 mg/dL and often under 70 mg/dL (Jacobson 2014) or reduction of ≥50% (Stone 2013). In order to reach these goals, lipid-lowering therapies are often taken in combination. The combination of bempedoic acid and a PCSK9 inhibitor (PCSK9i) may offer an additional treatment option in the future for physicians.

4.2. Background on Bempedoic Acid

4.2.1. Mechanism of Action

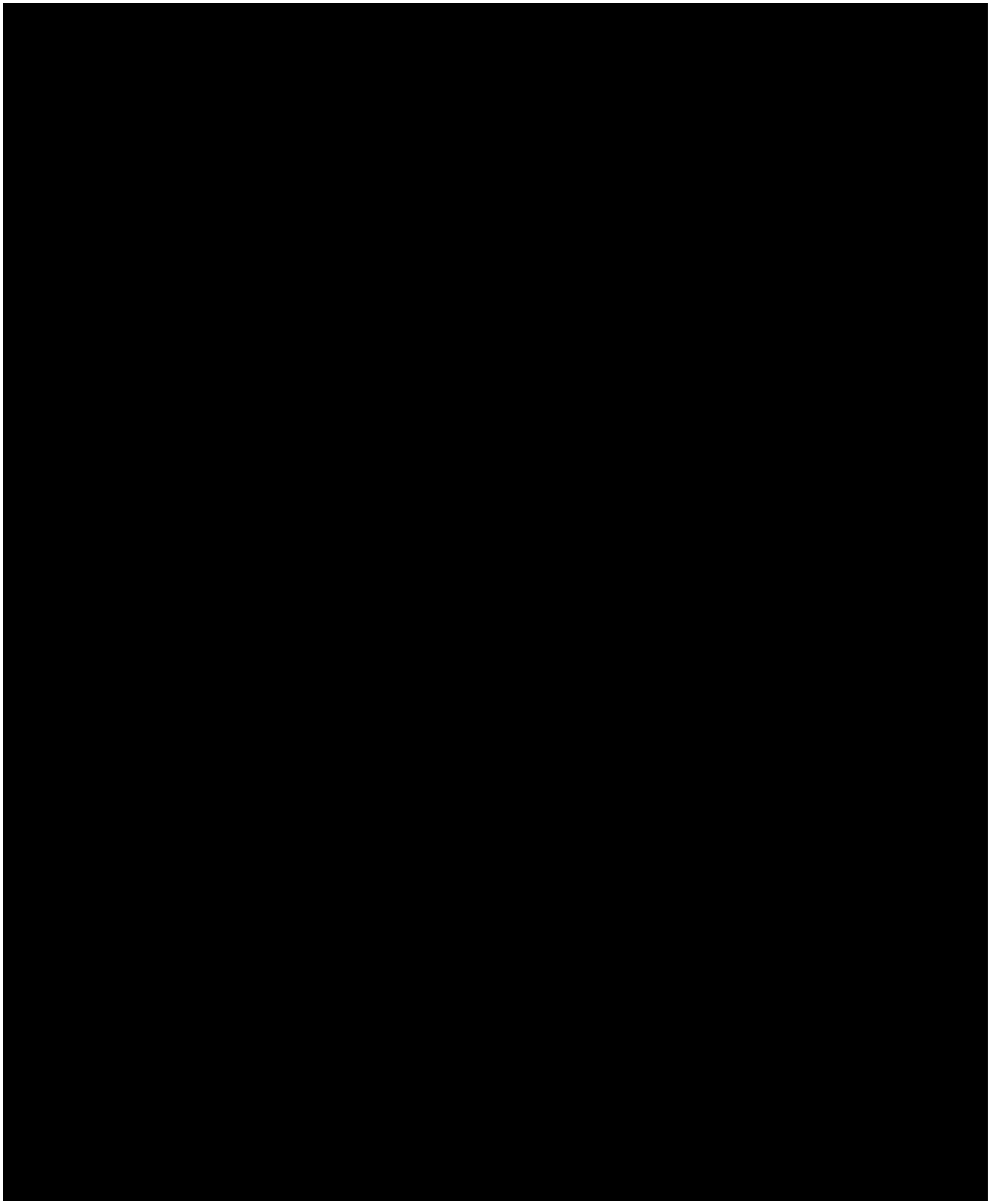
Bempedoic acid is a first-in-class small molecule inhibitor of ACL, an enzyme upstream of HMG-CoA in the cholesterol biosynthesis pathway. Bempedoic acid is a prodrug that requires activation in liver to ETC-1002-co-enzyme A (ETC-1002-CoA), which mediates competitive

inhibition of ACL. Inhibition of ACL by ETC-1002-CoA decreases cholesterol synthesis in liver leading to increased LDL receptor (LDLR) expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC-1002-CoA reduces LDL-C via the same pathway as HMG-CoA reductase inhibition by statins.

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

4.2.2. Nonclinical Experience

4.2.3. Previous Human Experience



[redacted]

4.2.4. Dose Selection

[redacted]

4.2.5. Background Therapy

Bempedoic acid in this study is currently being evaluated as an add-on to PCSK9i therapy.

4.2.6. Risk Benefit Summary

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

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

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Study Objectives

5.1.1. Primary Objective

- To assess the 2-month efficacy of bempedoic acid 180 mg/day vs placebo in the reduction of LDL-C in patients on PCSK9i therapy

5.1.2. Secondary Objectives

- To assess the 1-month efficacy of bempedoic acid 180 mg/day vs placebo in the reduction of LDL-C in patients on PCSK9i therapy
- To evaluate the effect of bempedoic acid 180 mg/day vs placebo on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and high-sensitivity C-reactive protein (hs-CRP) after 1 and 2 months in patients on PCSK9i therapy
- To evaluate the safety and tolerability of bempedoic acid 180 mg/day compared to placebo in patients on PCSK9i therapy

5.1.3. Exploratory Objectives

[redacted]

5.1.4. Primary Endpoint

The primary efficacy endpoint for this study is the percent change from baseline to Month 2 in LDL-C.

5.1.5. Secondary Endpoints

- Percent change from baseline to Month 1 in LDL-C
- Change from baseline to Months 1 and 2 in LDL-C
- Percent change from baseline to Months 1 and 2 in ApoB, non-HDL-C, TC, and hs-CRP
- Safety and tolerability of bempedoic acid in this patient population over 2 months, as assessed by AEs and clinical laboratory values

5.1.6. Exploratory Endpoints

[redacted]

[redacted]

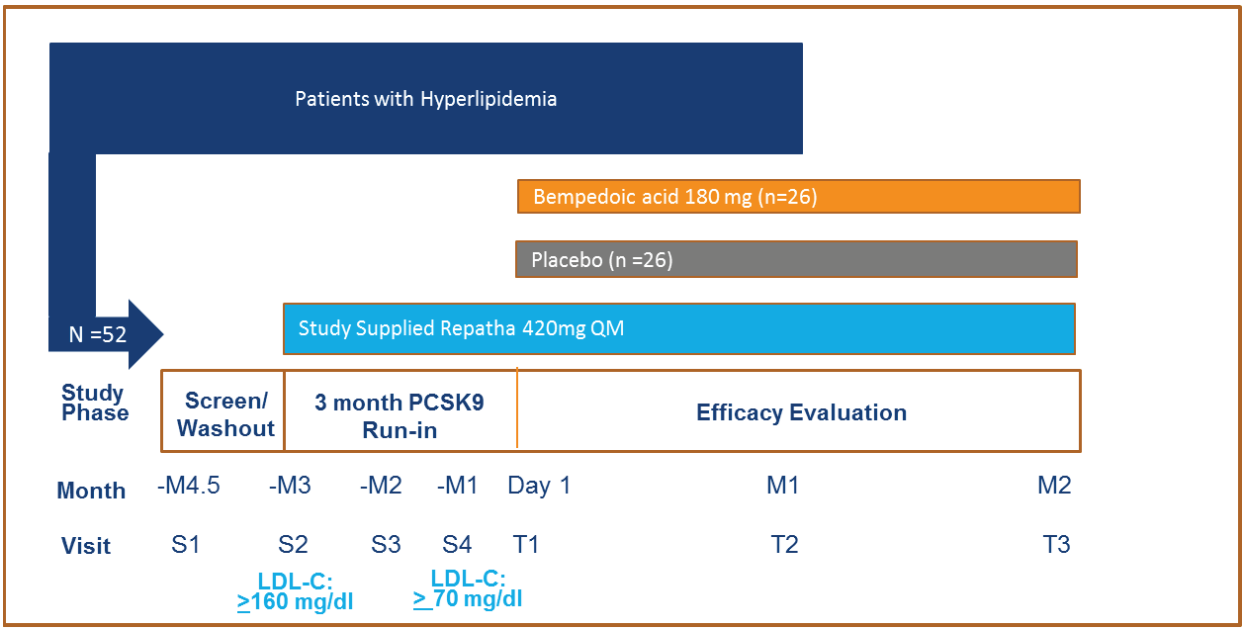
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 20 clinical sites in North America. Screening Month -4.5 (Visit S1) will occur approximately 18 weeks prior to randomization. After providing informed consent at Visit S1, patients will stop all background lipid-lowering therapy and lipid-modifying nutritional supplements, if applicable. All patients will return to the clinic on Month -3 (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate PCSK9 background therapy (Repatha 420 mg once montly [QM]). Sites that do not use a local lab may need to bring patients back for another visit to administer PCSK9 background therapy, as a qualifying LDL value is required prior to initiating the 3-month PCSK9i run-in period. No other background lipid-modifying therapy except study provided PCSK9i will be permitted during the trial. After 1 month (at least 30 ± 3 days), patients will return to the clinic for Month -2 (Visit S3) followed by Month -1 (Visit S4) 30 ± 3 days later. During these visits, Repatha will be administered, labs will be collected, and safety assessed. At Visit S4, LDL-C will be checked a second time prior to randomization. Patients with an LDL-C ≥70 mg/dL (via central lab only) at this visit will qualify for randomization. Patients with LDL-C <70 mg/dL at Visit S4 will be screen failed and no further PCSK9i therapy will be administered. Day 1 should occur 30 days ± 3 days after Visit S4, once LDL-C eligibility is established. On Day 1, qualified patients will be randomized 1:1 to bempedoic acid 180 mg/day (n = 26) or matching placebo (n = 26). Randomized patients will return for clinic visits at Month 1 (Visit T2) and Month 2 (Visit T3). Both study drug and PCSK9i doses will be administered on site during clinic visits after all procedures have been completed.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data across the bempedoic acid program.

Figure 1. Study 1002-039 Study Design



6.2. Study Hypothesis

The primary hypothesis is that bempedoic acid will result in greater reduction of LDL-C, as defined by the mean percent change from baseline at Month 2, than placebo when used in combination with a PCSK9i in patients with hyperlipidemia.

6.3. Study Duration and Period

The duration of treatment will be 26 weeks (1.5-month screening period, a 3-month lipid-stabilization period, and 2-month treatment period).

6.4. End of Study

The study will end when the last randomized patient completes the Month 2 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 10.5 months.

6.5. Number of Patients

The study will enroll approximately 52 adult patients with hyperlipidemia

6.6. Patient Identification Numbers

A unique patient identification number will be assigned to each patient by the interactive web response system (IWRS) at the time of informed consent and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, their patient identification number cannot be assigned to another patient.

6.6.1. Screening and 1 Month PCSK9i Run-in Period

Screening will occur approximately 18 weeks prior to Day 1 (Visit T1). Eligible patients will return to the clinical site at Month -3 (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate study-provided PCSK9i background therapy (Repatha 420 mg QM). No other background lipid-modifying therapy except study provided PCSK9i will be permitted during the trial.

Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel regarding their eligibility status and considered screen failures. As necessary, for reasons of safety if a patient begins the run-in period but screen fails prior to randomization, the patient may be asked to return to the clinical site for further evaluation and follow-up of AEs.

6.6.2. Randomization and Treatment Period

Patients who satisfy all entry criteria, complete the 1.5-month screening period and 3-month PCSK9i run-in period, and have an LDL-C ≥70 mg/dL at S4 will be randomized. Randomization numbers will be assigned via IWRS on Day 1 (Visit T1). Patients will be randomized in a ratio of 1:1 to receive 1 of the following 2 treatments in a double-blind fashion in addition to monthly PCSK9i background therapy:

- Bempedoic acid 180-mg tablet
- Matching placebo tablet

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Subject Inclusion Criteria

1. Provision of written informed consent must be obtained prior to any study-specific procedure.
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Month -4.5 (Visit S1)
3. Fasting, calculated LDL-C at screening (Visit S2) ≥160 mg/dL and ≥70 mg/dL at Visit S4

   Note: A single repeat of LDL-C may be completed. For those patients who have a repeat LDL-C, the average of the 2 values will be used to determine eligibility.
4. Men and nonpregnant, nonlactating women. Women must be:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      – ≥55 years, **or**
      – <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; **or**
   c. Women of childbearing potential willing to use 2 acceptable methods of birth control including:
      – oral, implanted, topical or injectable birth control medications
      – placement of an intrauterine device with or without hormones
      – barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
      – vasectomized male partner who is the sole partner for this patient
      – true abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)

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

7.2. Subject Exclusion Criteria

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

1. Homozygous Familial Hypercholesterolemia (HoFH)

2. Total fasting TG ≥500 mg/dL (5.6 mmol/L) at Month -3 (Visit S2)

   Note: A single repeat of TG may be completed prior to initiation of the single-blind Run-in period. For those patients who have a repeat TG, the average of the 2 values will be used to determine eligibility.

3. Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Month -4.5 (Visit S1)

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the average of the 2 values be used to determine eligibility.

4. All patients with known cardiovascular disease (CVD) or peripheral arterial disease (PAD) or cerebrovascular disease (CD)

5. History of type 1 or type 2 diabetes or laboratory evidence of diabetes (fasting blood glucose [FBG] ≥126 mg/dL or glycosylated hemoglobin, Type A_{1C} (HbA_{1C}) >6.5%) without prior diagnosis of diabetes at Month -4.5 (Visit S1)

6. Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg at Month -4.5 (Visit S1)

7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Month -4.5 (Visit S1)

8. Liver disease or dysfunction, including:

   a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Month -4.5 (Visit S1).

   b. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Month -4.5 (Visit S1).

      Note: If total bilirubin (TB) ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, the patient may be enrolled in the study.

      Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed. For those patients who have a repeat ALT and/or AST, the average of the 2 values will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but reflexive test for Hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.

9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption

10. History of hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Month -4.5 (Visit S1)

11. History of malignancy (except non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ)

12. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other meds for chronic pain that have been stable, without evidence of abuse prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
14. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood transfusion, or major surgery with or without blood loss within 30 days prior to randomization
15. Use of any experimental or investigational drugs within 30 days or 5 half-lives, whichever is longer
16. Previous enrollment in an Esperion Phase 3 bempedoic acid (ETC-1002) clinical study
17. Use of a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to screening, such as: anacetrapib, dalcetrapib or evacetrapib
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Month -4.5 [Visit S1]),
    - Lomitapide or apheresis therapy (must be stopped at least 3 months prior to Month -4.5 [Visit S1]),
    - Red yeast rice containing products (must be stopped on or before Month -4.5 [Visit S1]),
    - Lipid regulating drugs or supplements (must be stopped on or before Month -4.5 [Visit S1])
19. Planned initiation or changes to the following drugs prior to Month -4.5:
    - Hormone replacement (6 weeks prior to Month -4.5)
    - Thyroid replacement (6 weeks prior to Month -4.5)
    - Obesity medication (3 months prior to Month -4.5)
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study
21. Patient is pregnant or breast feeding, or planning to become pregnant during treatment and/ or within 30 days after the end of treatment
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
23. Heterozygous familial hypercholesterolemia (HeFH)
24. Concomitant use of a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at (Visit S1) or prior use within the past 16 weeks of Visit S1

7.3. Investigator/Sponsor Suspension or Termination of Patient Enrollment

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

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

Possible reasons for termination of the study at a clinical site include, but are not limited to:

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

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

8. TREATMENT OF PATIENTS

8.1. Description of Investigational Medicinal Product

Table 2: Investigational Medicinal Products

Product Name:	Bempedoic acid	Placebo to Match Bempedoic Acid
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure[a]	35-count bottle with screw on childproof cap	35-count bottle with screw on childproof cap
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):		

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

Please see Pharmacy Manual for detailed storage requirements and instructions.

8.2. Concomitant Medications

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

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

8.2.1. Prohibited Lipid-Regulating Medications and Dietary Supplements

- Patients will be required to stop taking all prescription or nonprescription drugs or dietary supplements taken for the purpose of lipid regulation at Month -4.5. With the exception of the study provided PCSK9i (Repatha 420 mg QM), no other lipid-modifying therapies or supplements will be permitted.

8.2.2. Allowable Medications

- Hormone replacement (if stable 6 weeks prior to Month -4.5)
- Thyroid replacement (if stable 6 weeks prior to Month -4.5)
- Obesity medication (if stable 3 months prior to Month -4.5)

8.3. Blinding

Patients who satisfy all entry criteria during the screening phase and complete the PCSK9i run-in period will be randomized to a treatment group at Day 1 (Visit T1). The Investigator or designee will contact IWRS at this visit to randomize the patient into the study. The IWRS will determine the randomized treatment assignment number and the appropriate study drug container via medication identification numbers (MED ID). A patient is considered to be randomized when they have been assigned a MED ID number by IWRS.

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

Blinding of treatment must be maintained for all patients unless, in the opinion of the Investigator, the safety of the patient may be at risk. Only under the rarest of circumstances should the Investigator consider breaking the blind and only when medical/supportive care cannot be provided without determining if the patient is receiving active drug treatment. In the event that the blind needs to be broken prior to completion of the study, the Investigator should contact the appropriate Medical Monitor by telephone. If the blind must be broken prior to consultation with the Medical Monitor, contact must be made within 24 hours of breaking the blind. At the initiation of the study, the clinical site will be instructed on procedures for breaking the blind via the IWRS. In all cases of breaking the blind, the Investigator must document in the patient's medical record the date, time, and reason for breaking the blind, and the names of personnel involved.

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

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

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

8.4. Overdose

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

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1. Investigational Medicinal Product Supply and Control

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

PCSK9i will be provided as background therapy. This will be dispensed and administered during clinic visits and will be stored and taken as commercially labeled.

The MED ID number (an identifier on the study drug packaging) will be obtained via IWRS and used to select PCSK9i and double-blind IMP for the treatment period from available clinical supplies at the clinical site.

Double-blind IMP will be dispensed in 35-day supply increments to patients by appropriate clinical site personnel. Patients will receive one 35-day supply bottle at Day 1 (Visit T1) and at Month 1 (Visit T2).

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

9.2. Administration of Investigational Medicinal Product

Patients will be instructed to ingest IMP starting at Visit T1 for the duration of treatment period orally once daily (once every 24 hours) at approximately the same time each day with water. IMP may be taken with or without food. On clinic visit days, patients will be instructed to delay ingestion of IMP until all study procedures have been completed. If a patient arrives at clinic on Visits T1, T2, or T3 without having fasted or having taken IMP before arriving at the clinic, reschedule the visit (the next day or as soon as possible) so that the fasting and dosing requirements have been met. Patients will be instructed to return all packaging and unused IMP at each clinic visit.

If the patient forgets to take IMP at the usual time on nonclinic visit days, it may be taken up to 12 hours later the same day. After that time, the patient should not take IMP that day and should resume ingestion of IMP the following day. If a patient fails to take IMP, details describing the reasons for nondosing should be documented in the patient's medical records and eCRF. Extra IMP (7 extra days per bottle) is provided and can be used, if needed, prior to the next visit or to replace a dose of IMP that cannot be used because it is lost or damaged.

PCSK9i will be administered on site at Visits S2, S3, S4, T1, and T2. Doses will be stored and administered as required in prescribing information

9.3. Investigational Medicinal Product Accountability

Accurate records of the receipt of all IMP and PCSK9i shipped by the Sponsor (or designee) and the disposition of the IMP and PCSK9 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/PCSK9i inventory (including entry/movement/disposition)
- Date and amount of IMP/PCSK9i dispensed to each patient, including unique patient identifiers
- Date that IMP/PCSK9i was returned by patient, assessment of compliance, and relevant documentation of discrepancies
- Nonstudy disposition (eg, lost, broken, wasted)
- Amount returned to Sponsor/Sponsor's designee/destroyed or amount destroyed per local standard operating procedure (SOP) following accountability by site monitor.

9.4. Investigational Medicinal Product Handling and Disposal

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

10. STUDY PROCEDURES

10.1. Informed Consent

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

10.2. Procedures and Schedule of Assessments

Patients who provide informed consent and sign the ICD will be eligible to begin screening for the study. The study is comprised of 3 distinct periods: screening, PCSK9i run-in and double-blind treatment.

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

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

10.2.1. Screening Month -4.5 (Visit S1)

The screening period will begin with a screening visit that will occur approximately 18 weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history
- Concomitant and prohibited medication review
- Height (cm), weight (kg), body mass index (BMI)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - HbA_{1C}
  - TSH
  - FSH (in appropriate female patients)
  - Serum pregnancy test (on appropriate female patients)
- Serology (including HBsAg, Hepatitis C virus [HCV])

- Review of all inclusion/exclusion criteria that can be assessed at this time
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

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

10.2.2. PCSK9i Run-in Month -3 (Visit S2)

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

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

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination (PE)
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
- ApoB and hs-CRP
- First PCSK9i monthly injection. Verification of lipid entry criteria (LDL-C value of >160 mg/dL and triglycerides <500 mg/dL) must be obtained before starting PCSK9i
- Schedule next visit **(S3 has to be at least 30 days ± 3 days from the first dose of PCSK9)**
  - PCSK9i injections must be administered consistently throughout the trial within 30 ± 3 days from the previous dose. Efficacy will vary if the doses are not consistently administered.

Note: Local labs can be used to assess LDL-C and TGs for entry. All other labs must be run via the central lab. If using a central lab or a local lab with a delay in obtaining results, an optional visit to administer PCSK9 may be scheduled. **Patients need to be on Repatha 420 mg for at least 30 days ± 3 days before conducting Visit S3.**

10.2.3. PCSK9i Run-in Month -2 (Visit S3)

Prior to scheduling Visit S3, review the screening clinical results to evaluate whether the patient continues to meet eligibility criteria.

- If the patient continues to meet eligibility criteria, then schedule Visit S3 and proceed with Visit S3 procedures

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Vital signs
- Basic fasting lipids (TC, calculated LDL C, [redacted] non-HDL C, [redacted], and [redacted])
- PCSK9i monthly injection must be given at the end of procedures

10.2.4. PCSK9 Run-in Month -1 (Visit S4)

One month (30 ± 3 days) from S3, patients will have their LDL-C evaluated a second time via **central lab only** prior to randomization on Day 1.

The patient will undergo the following assessments and procedures at (Visit S4)

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Vital signs
- Basic fasting lipids (TC, calculated LDL C, [redacted], non-HDL C, [redacted], and [redacted])
- Schedule next visit Day 1 **(Day 1 should occur 30 ± 3 days after S4, once LDL-C eligibility [≥70 mg/dL] is established)**
- PCSK9i monthly injection must be given at the end of procedures

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

Prior to scheduling Visit T1, review S1, S2, S3, and S4 clinical results to evaluate whether the patient continues to meet eligibility criteria.

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

If the patient has met all inclusion criteria, none of the exclusion criteria, and has been on Repatha 420 mg **for 30 ± 3 days during each month of the PCSK9 run-in period**, the patient may be randomized into the double-blind treatment period. Patients who fail to meet any entry criterion prior to randomization are considered to be screen failures, will not be randomized into a treatment group, and are not required to return for additional visits. Patients are considered randomized once all eligibility criteria are confirmed and a randomization number is obtained by the IWRS on the day of first dose.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis

    Note: Urine pregnancy test (for females of childbearing potential)
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ApoB and hs-CRP
  - HbA_{1C}
- Predose PK
- Review inclusion/exclusion criteria to establish patient eligibility. **Patient must have an LDL-C ≥70 mg/dL at S4 before they can be randomized on Day 1.**
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions (35-day supply bottles)
  - **Subject should be randomized and receive IMP within 30 ± 3 days of S4, as soon as the final LDL-C entry criterion is met**
- PCSK9i injection and IMP must be given at the end of procedures
- Schedule next visit

10.2.6. Treatment Month 1 (Visit T2 ±3 days)

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

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

Patients will undergo the following assessments and procedures at Month 1 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis

  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ApoB and hs-CRP
- Predose PK. Should be taken ideally within 4 hours of the patient's normal time of dosing
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Dispense IMP and provide dosing instructions (35-day supply bottles)
- PCSK9i injection and IMP must be given at the end of procedures
- Schedule next visit

10.2.7. Treatment Month 2 (Visit T3 ±3 days)/EOS

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

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

Patients will undergo the following assessments and procedures at Month 2 (Visit T3):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- PE
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ApoB and hs-CRP
  - HbA_{1C}
- Predose PK. Should be taken ideally within 4 hours of the patient's normal time of dosing
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Complete study status in IWRS (ie, completed study).

10.3. Subject Withdrawal Criteria

10.3.1. Early Withdrawal from the Study

Patients must remain in the study until the last scheduled visit at Month 2 (Visit T3) to be considered as having completed participation in the study.

Patients who temporarily withdraw from IMP prior to Month 2 (Visit T3) for any reason may restart IMP providing that 1) the patient and the investigator are in agreement regarding this course of action, 2) the patient has been off of IMP for 2 weeks or less; and 3) IMP can be started as soon as possible. For cases where the patient has been off of IMP for more than 4 weeks, the investigator must contact the medical monitor for approval prior to restarting IMP.

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

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

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

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

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

10.3.2. Procedures for Early Withdrawal

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

All effort should be made to have each patient complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed. Except in the case of a medical emergency, the procedures and assessments detailed in Section 10.2.7 will be performed upon the discontinuation of the study.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

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

11.1.1. Demographic/Medical History

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

11.1.2. Vital Signs

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

The patient should sit quietly for 5 minutes prior to collection of vital signs. At all time points, vitals will be collected prior to blood collection. Blood pressure (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.

11.1.3. Weight, Height, and Body Mass Index

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

Height will be measured using standard clinic procedures.

BMI will be calculated using the formula:

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

11.1.4. Physical Examination

PEs will include an assessment of the following:

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

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

Note: Additional information will be collected regarding muscle-related AEs. See Section 12.3.

11.1.5. Clinical Laboratory Tests

11.1.5.1. Laboratory Parameters (Safety)

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

Table 3: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %)	Blood Chemistry (serum, fasting) • Albumin (Alb) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB)[a] • Total protein • Uric acid Coagulation—only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at T1 and 3 to 5 days post-T1 • Prothrombin time (PT) • International normalized ration (INR)
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Additional samples • Hemoglobin A_{1C} (HbA_{1C}) • PK

Table 3: Clinical Laboratory Parameters (Safety)

Clinical Laboratory Test	Clinical Laboratory Test
Other Screening Labs • Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV)[b] • Serum pregnancy test (only for females of childbearing potential) • Follicle-stimulating hormone (FSH; Females <55 years and >1 year without menses) • Urine pregnancy test prior to randomization (for female of child bearing potential) • Thyroid-stimulating hormone (TSH)	

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

11.1.5.2. Clinical Laboratory Tests (PK)

Trough PK plasma concentrations of bempedoic acid and its metabolite ESP15228 will be collected prior to dosing at Visits T1, T2, and T3. See lab manual for additional details.

Patients will be in a seated position during the blood collection. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping are described in Section 11.1.5.3.

11.1.5.3. Sample Collection, Storage, and Shipping

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

Blood draws for lipids, [redacted], and glucose must meet the criteria listed below. If these criteria have not been met, these blood samples will NOT be collected. If these criteria can be met by rescheduling the clinic visit to occur within 3 days, the lipid, [redacted], and/or glucose blood samples will be collected at the rescheduled clinic visit only.

- Blood samples will be drawn after a minimum 10-hour fast (water is allowed)

11.1.5.4. General Monitoring and Management of Abnormal Clinical Labs

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

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the patient, the Investigator should determine if it qualifies as an AE, and if yes, an appropriate eCRF will be completed. All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause or resolution. Specific monitoring and management guidelines for laboratories of special interest are outlined in the sections below.

11.1.5.4.1. Monitoring and Management of Elevated Liver Function Tests

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

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

- If repeat LFT assessment confirms ALT and/or AST >3 × ULN, consideration should be given to withdrawing the patient and administering no further doses of study drug. At the investigator's discretion, study drug may be interrupted and the patient rechallenged with study drug after LFTs have returned to baseline levels.
- If repeat LFT assessment confirms ALT and/or AST >5 × ULN, patient should be withdrawn from IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1).
- If repeat LFT assessment confirms ALT and/or AST >3 × ULN in addition to any of the following, the patient should be given no further IMP treatment, but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1):
  - TB >2 × ULN

    Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of 2 × ULN will be based upon direct (conjugated) bilirubin.
  - INR >1.5 × ULN (unless the patient is on stable dose of anticoagulation medication)
  - Appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia

11.1.5.4.2. Monitoring and Management of Elevated Serum Creatinine

If at any time after randomization, a patient experiences a decrease in eGFR to the level of 15 mL/min/1.73 m^2) or if the patient experiences acute renal failure, the patient should be withdrawn from IMP treatment but will be asked to continue to be followed for safety using the protocol-specified visit schedule (see Appendix 1)

11.1.5.4.3. Monitoring and Management of Elevated Creatine Kinase

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

Repeat CK assessment will include query for related symptoms.

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN, if asymptomatic, the patient should receive further assessment and investigation into the cause, assess whether there is renal injury, and measure CK approximately weekly or more frequently if clinically indicated until resolution. If CK levels continue to rise; IMP should be discontinued.
- If symptomatic, the following should be completed:
  - Hold IMP
  - Clarification of the nature, duration, and intensity of muscle symptoms
  - Review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology)
  - Evaluation for additional diagnoses or other conditions which can cause myopathy including muscle tenderness (by PE), weakness, rash, measurement of serum creatinine, dipstick urinalysis with microscopy if indicated
  - Obtain clinical chemistries to assess the possibility of lactic acidosis
  - Follow symptoms and CK until the abnormality has resolved
  - If based on the above evaluation an alternative explanation is suspected, consideration can be given to resuming IMP once CK returns to baseline levels
  - If no alternative explanation exists, consideration should be given to withdrawing the patient from IMP treatment.
- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality as listed below, the patient should be withdrawn and given no further doses of study drug:
  - >10 × ULN, even in the absence of symptoms.
  - In all cases, evaluate the signs/symptoms and laboratory evaluations as outlined above.

- If the patient is withdrawn from IMP treatment, the patient should be asked to continue being followed for safety using the protocol-specified visit schedule (see Appendix 1).

11.1.5.5. Monitoring and Management of Potential Hypoglycemia and Metabolic Acidosis

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

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

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

12. ADVERSE AND SERIOUS ADVERSE EVENTS

12.1. Adverse Events

12.1.1. 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 adverse events 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, 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 study drug administration, as defined in the Statistical Analysis Plan (SAP).

12.1.2. 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).

12.1.3. Reporting for Adverse Events

All AEs occurring during the course of the study (starting from signing informed consent through 30 days after last dose of study treatment) 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. 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" if that is the final diagnosis). 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 the AE, not the procedure itself.

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.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs, as described below. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. 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.

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

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 or PCSK9i.

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.

12.1.4. 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.

12.1.5. 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 rechallenge.

12.1.6. 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, until deemed stable/chronic, or for 30 days after study completion, whichever comes first, with the exception of patients reporting SAEs (see Section 12.2.2).

12.1.7. Treatment-Emergent Adverse Events

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

12.2. Serious Adverse Events

12.2.1. 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 inpatient 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 criteria, 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.

Events or Outcomes Not Qualifying as Serious Adverse Events

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

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

12.2.2. 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 of 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 also reported to the Sponsor.

To report the SAE, the SAE information should be entered on to the AE eCRF in the EDC database 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/IEC in accordance with local requirements. All investigators involved in studies using the same investigational product will receive any safety alert notifications for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

All SAEs should be recorded on the eCRF and source documents. Criteria for documenting the relationship to 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 information on the AE eCRF 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, IECs/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 IEC/IRB of SAEs occurring at their site and other SAE reports received from the Sponsor, in accordance with local procedures and statutes.

12.2.3. Reporting of Patient Death

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

12.2.4. Reports of Pregnancy and Lactation

Although not considered an SAE (unless an event occurs with a serious outcome), any event of pregnancy will be collected by the designated Safety contact. If a female patient should become pregnant during the course of the study or within 30 days after last dose of study treatment, the Principal Investigator or designee must contact the designated Safety contact within 24 hours of knowledge of the pregnancy. In addition, a paper 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 paper Pregnancy Outcome Report Form must be completed and submitted to the Safety contact. Patients who are breastfeeding are excluded from this study and should discontinue study medication.

12.3. 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.

12.4. Data Monitoring Committee

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

12.5. Assessment of Lipid Endpoints

12.5.1. Lipid Parameters

After randomization, patients will return to clinic every month. Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, [redacted] TC, ApoB, [redacted] and [redacted] at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

12.5.2. Clinical Laboratory Tests (Lipids)

Clinical laboratory samples will be collected at all clinic visits.

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

- Blood samples will be drawn after a minimum 10-hour fast (water is allowed)

Patients are encouraged to be in a seated position during the blood collection. Clinical laboratory parameters and tests will include those listed in Table 4. Collection schedule and instructions are provided in the Clinical Laboratory Manual. A description of the sample collection, storage, and shipping as well as monitoring and management of abnormal laboratories are described in Section 11.1.5.

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

Table 4: Clinical Laboratory Parameters (Lipids) and Cardiometabolic Biomarkers

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

13. STATISTICS

13.1. General Considerations

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

Summary statistics for continuous variables will include the number of patients, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

13.2. Determination of Sample Size

The planned total sample size for this study is 52 with 26 patients in the bempedoic acid 180 mg group and 26 in the placebo group. This sample size is expected to [redacted]

13.3. Analysis Populations

The Full Analysis Set (FAS), used for all of the efficacy analyses, is defined as all randomized patients with a baseline lipid value, at least 1 postbaseline lipid value, and having taken their study drug within 2 days of the lipid measurement. The FAS is also known as the modified intention-to-treat (mITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received. Other subsets of the FAS will be considered to evaluate primary and secondary endpoints as sensitivity analyses and the details will be described in the SAP.

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.

13.4. Disposition, Demographics, and Baseline Characteristics

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

13.5. Primary Endpoint

The primary efficacy endpoint is the percent change from baseline to Month 2 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with

treatment group as a factor and baseline LDL-C as a covariate. The details of the ANCOVA model and options to correct for unequal variances will be described in the SAP. Baseline LDL-C is defined as the average of S4 and Day 1 values, if only 1 value is available, then that single value will be used as baseline. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Patients who are missing their Month 2 LDL-C will have their Month 2 value imputed by last observation carried forward (LOCF). The least squares mean (LSM) and standard error (SE) for percent change estimate will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

The ANCOVA assumptions will be examined and nonparametric test or transformation of the data will be considered if these assumptions are not met.

13.6. Secondary and Exploratory Efficacy Endpoints

The secondary efficacy endpoints (percent change from baseline to Month 1 in LDL-C; change from baseline to Months 1 and 2 in LDL-C; percent change from baseline to Months 1 and 2 in ApoB, non-HDL-C,TC, hs-CRP [redacted] and [redacted]), will be analyzed using the ANCOVA method similar to the primary endpoint. Baseline value for TC, non-HDL-C, [redacted] will be the average of S4 and Day 1 values; ApoB and hs-CRP will be the Day 1 value, if only 1 value is available, the single value will be used as the baseline. Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Missing values will be imputed using LOCF, where applicable. For each parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p value.

All efficacy endpoints will be analyzed at a significance level of 0.05, no multiplicity adjustment will be implemented.

Exploratory endpoints will be summarized by descriptive statistics.

13.7. Safety Endpoints

The safety analyses for this study will be descriptive in nature, no statistical inferences are planned

The subject incidence of all TEAE, SAEs, related AEs, AEs leading to withdrawal of study drug and/or study, fatal AEs, and AESI will be tabulated by system organ class (SOC) and preferred term in descending order of frequency and by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, HbA_{1C}, 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 postbaseline time point.

Hepatic Safety

For liver-associated enzymes and TB, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. All liver-associated laboratory abnormalities will be assessed for Hy's Law criteria (≥3 × ULN for either ALT or AST, with accompanying TB >2 ×

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

Musculoskeletal Safety

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

Diabetes/Hyperglycemia

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

Renal Safety

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

Neurocognitive Events

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

13.8. Pharmacokinetics

Three trough plasma concentrations of bempedoic acid and ESP15228 will be collected and summarized from patients at predose (T1), T2, and T3 for use in further developing the population PK model.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

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

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

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

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

14.2. Audits and Inspections

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

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

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor / designee may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Institutional Review Board/Independent Ethics Committee Approval

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

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

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

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

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

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

16.2. Ethical Conduct of the Study

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

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

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

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

16.3. Written Informed Consent

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

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

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

16.4. Patient Confidentiality

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

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

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

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

17.3. Case Report Forms and Study Records

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

Study records are comprised of source documents, eCRFs, and all other administrative documents (eg, IRB or IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, and correspondence). A study-specific binder will be provided with instructions for the maintenance of study records.

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

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

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

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

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

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

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

18. ADMINISTRATIVE CONSIDERATIONS

18.1. Investigators

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

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

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

18.2. Amendments

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

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

18.3. Financial Disclosure

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

19. PUBLICATION AND DISCLOSURE POLICY

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

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

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

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

20. LIST OF REFERENCES

Food and Drug Administration (2012). FDA announces safety changes in labeling for some cholesterol-lowering drugs [Press release]. Retrieved from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm293623.htm

Jacobson TA for the NLA Task Force on Statin Safety - 2014 update. J Clin Lipidol. 2014;8:S1-4.

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Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014; 35:2950-9.

Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Atherosclerosis Risk in Communities Study Group. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions. The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001;104:1108-13.

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merc CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a

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

21. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS (SUBJECT VISIT SCHEDULE)

	Schedule of Events						
Visit	**S1[1,2]**	**S2**	**S3**	**S4**	**T1**	**T2**	**T3/EOS)[3]**
Month	**Month -4.5**	**Month -3**	**Month -2**	**Month -1**	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day -135**	**Day-90 ±3**	**Day -60 ±3**	**Day -30 ±3**	**Day 1***	**Day31 ±3**	**Day61 ±3**
Informed Consent	X						
Enrollment Criteria	X	X	X	X			
Demographics	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X
Physical Exam		X					X
Weight[4]	X				X		X
Height	X						
Vital Signs[6]	X	X	X	X	X	X	X
Serology[7]	X						
Serum Pregnancy/FSH[8]	X						
Urine pregnancy test for women of childbearing potential only					X		
TSH	X						
Clinical Safety Labs[9]	X				X	X	X
Basic Fasting Lipids[10]	X	X**	X	X***	X	X	X
ApoB and hs-CRP		X			X	X	X

	Schedule of Events						
Visit	**S1[1,2]**	**S2**	**S3**	**S4**	**T1**	**T2**	**T3/EOS)[3]**
Month	**Month -4.5**	**Month -3**	**Month -2**	**Month -1**	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day -135**	**Day-90 ±3**	**Day -60 ±3**	**Day -30 ±3**	**Day 1***	**Day31 ±3**	**Day61 ±3**
HbA_{1C}	X				X		X
PK – predose trough					X	X	X
Diet and exercise counseling[11]	X	X			X	X	X
Establish Patient Eligibility					X		
Randomization					X		
IWRS Contact[12]	X				X	X	X
PCSK9i administered at site		X	X	X	X	X	
Double-blind Drug Dispensing					X	X	
IMP Return/Compliance						X	X
PCSK9i Return/Accountability		X	X	X	X	X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T4 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

[1] An optional basic fasting lipid MAY be completed prior to S2, but must occur just prior to the next witnessed PCSK9i dose if patient fails to meet lipid entry criterion at Visit S1. If this optional basic fasting lipid is completed, the average of the 2 lipid values will be used to determine eligibility.

[2] A recheck of blood pressure may be completed prior to T1 if the patient's diastolic blood pressure (DBP) and/or systolic blood pressure (SBP) meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. Repeat labs may be completed prior to T1 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either T3/EOS if completing the study or early withdrawal.

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

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

[7] Serology for HBsAg, HCV-ABVivi

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

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.

[10] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), [redacted] non-HDL-C,), and [redacted]).

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

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

* Patients must be on PCSK9 for 30 ± 3 days during each month of the PCSK9 run-in period before initiating Day 1.

** LDL-C must be ≥160 mg/dL and TG <500 mg/dL before initiating PCSK9i. A local lab may be used to assess LDL-C and TG for eligibility prior to initiating Repatha, but a central lab must also be conducted at this visit.

*** LDL-C must be ≥70 mg/dL to qualify for randomization. Only a central lab may be used to assess entry LDL-C.

APPENDIX 2. SPONSOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy

Study Number: 1002-039

Final Date: 05 March 2017

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: 3/8/17

Study Title:	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy
Study Number:	1002-039
Final Date:	05 March 2017

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

Signed:  Date: 9-March-2017

APPENDIX 3. INVESTIGATOR'S SIGNATURE

Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy

Study Number: 1002-039

Final Date: 05 March 2017

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

Signed: _____ Date: _____

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

APPENDIX 4. SUMMARY OF CHANGES IN AMENDMENT 1

SUMMARY OF CHANGES
CLINICAL STUDY PROTOCOL

Study Number:	1002-039
Study Title:	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD When added to proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitor Therapy
Protocol Version Incorporating Current Summary of Changes:	Amendment 1, 05 March 2017
Preceding Protocol Version:	Original Protocol, 22 November 2016
Investigational Product Name:	ETC-1002

Conventions used in this Summary of Changes Document

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

Summary and Justification of Changes

Below are the main protocol changes:

- The PCSK9 run-in was extended from 1 month to 3 months in order to ensure all patients reach steady state prior to randomization.
- Added/revised the following subject exclusion criteria to exclude patients that were recently on PCSK9 inhibitors as well as HeFH patients (this population will be studied in P3 trials):
  - Heterozygous Familial Hypercholesterolemia (HeFH)
  - Concomitant use of a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at (Visit S1) or prior use within the past 16 weeks of Visit S1

  - Use of any experimental or investigational drugs within 30 days ***or 5 half-lives, whichever is longer***

- Updated contraception language to align with other P3 ETC-1002 clinical trials.
  - Added requirement that women use 2 rather than 1 form of acceptable contraception; expanded definition of true abstinence.
- Removed remnant ECG language. There are no ECG assessments, these were inadvertently added to the original protocol
- Removed evaluation of PCSK9 levels from exploratory objectives and endpoints
- Specified that LDL-C levels used for evaluation for study inclusion can use a local lab at S3, but that S4 evaluation can only use a central lab

CHANGE 1 REVISION OF PROTOCOL TITLE AND TITLE PAGE VERSION INFORMATION

Location:

Protocol title

Original Text:

A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy

New Text:

A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to ***Proprotein Convertase Subtilisin/Kexin Type 9 (***PCSK9***)***-Inhibitor Therapy

Location:

Title page

Original Text:

Version	Date
Original Protocol:	22 November 2016

New Text:

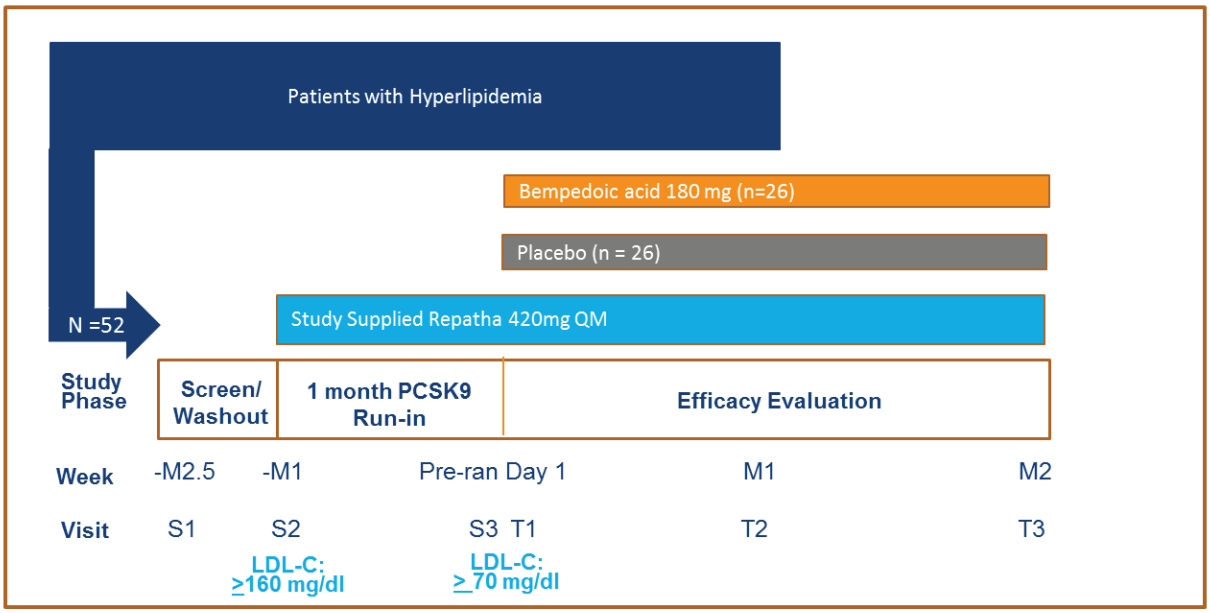
Version	Date
Original Protocol	22 November 2016
Protocol Amendment 1:	***05 March 2017***

CHANGE 2 STUDY DESIGN FIGURE REVISIONS

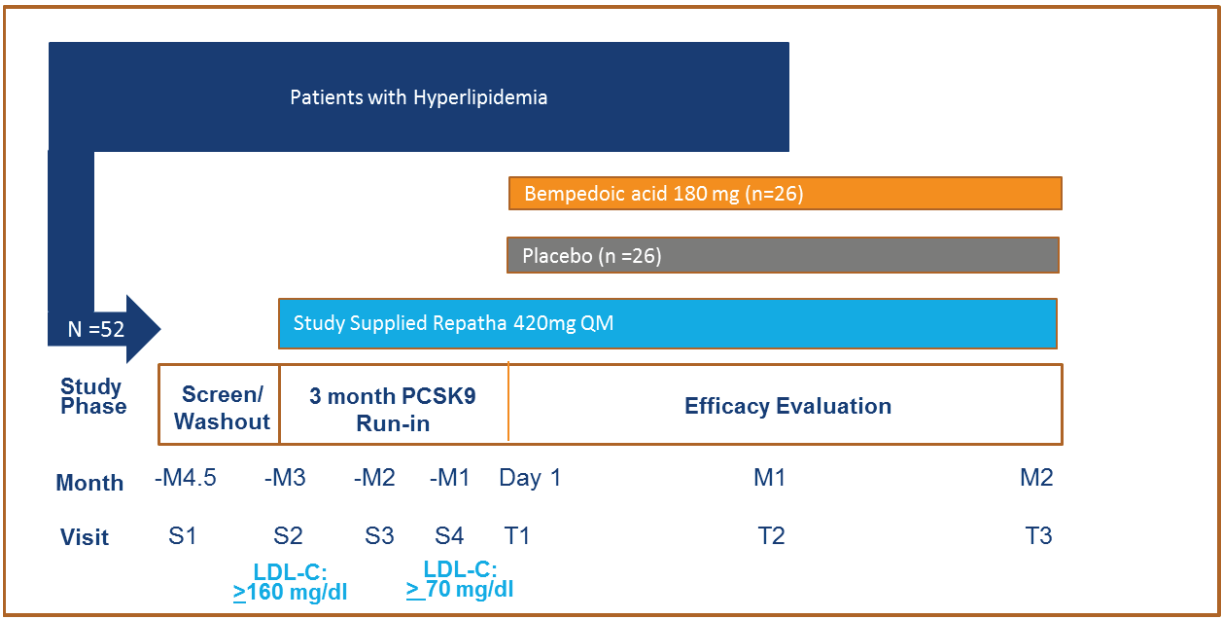
Location:

Section 2. Synopsis and Section 6.1. Overall Study Design

Original Text:



New Text:

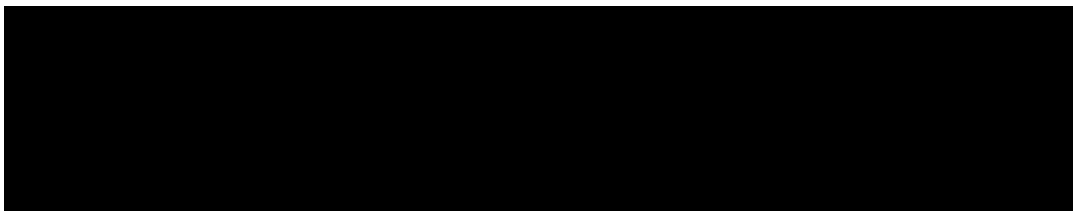


CHANGE 3 STUDY OBJECTIVES REVISIONS

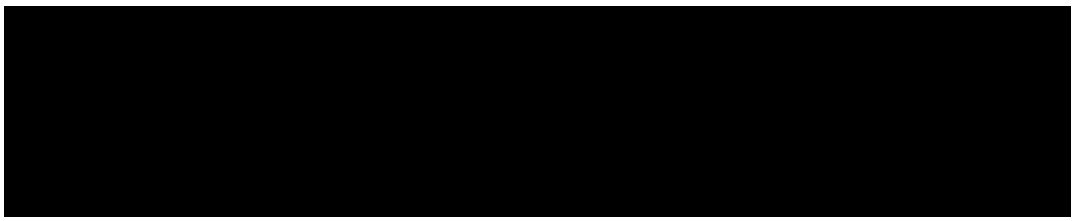
Location:

Section 2, Synopsis;
Section 5.1.3, Exploratory Objectives;
Section 5.1.6, Exploratory Endpoints

Original Text:



New Text:



CHANGE 4 STUDY METHODOLOGY REVISIONS

Location:

Section 2, Synopsis;
Section 6.1, Overall Study Design

Original Text:

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 20 clinical sites in North America. Screening Month -2.5 (Visit S1) will occur approximately 10 weeks prior to randomization. After providing informed consent at Visit S1, patients will stop all background lipid-lowering therapy and lipid-modifying nutritional supplements, if applicable. All patients will return to the clinic on Week -4 (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate PCSK9 background therapy (Repatha 420 mg QM). Sites that do not use a local lab may need to bring patients back for another visit to administer PCSK9 background therapy, as a qualifying LDL value is required prior to initiating background therapy. No other background lipid-modifying therapy except study provided PCSK9 will be permitted during the trial. After a 1-month (at least 30 days) PCSK9i lipid-stabilization period, patients will return to the clinic for Visit S3. The sole purpose of this visit is to determine entry LDL-C prior to randomization. Patients with an LDL-C ≥70 mg/dL (via central or local lab) at this visit will qualify for randomization. Patients with LDL-C <70 mg/dL at Visit S3 will be screen failed and no further PCSK9i therapy will be administered. Day 1 should occur immediately (ideally within 3 days) after Visit S3, once LDL-C eligibility is established. On Day 1, qualified patients will be randomized 1:1 to bempedoic acid 180 mg/day (n = 26) or matching placebo (n = 26). Randomized patients will

return for clinic visits at Month 1 (Visit T2) and Month 2 (Visit T3). Both study drug and PCSK9i doses will be administered on site during clinic visits after all procedures have been completed.

New Text:

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 20 clinical sites in North America. Screening Visit S1 will occur approximately ~~2.5~~***4.5*** months prior to randomization. After providing informed consent at Visit S1, patients will stop all background lipid-lowering therapy and lipid-modifying nutritional supplements, if applicable. All patients will return to the clinic on Month -***3***~~1~~ (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate PCSK9i background therapy (Repatha 420 mg ***once monthly [***QM***]***). Sites that do not use a local lab may need to bring patients back for another visit to administer PCSK9i background therapy, as a qualifying LDL-C value is required prior to initiating ***the 3-month PCSK9i run-in period***~~initial background therapy~~. No other background lipid-modifying therapy except study-provided PCSK9***i*** will be permitted during the trial. After ~~a~~ 1 month (at least 30 days ***±3 days***) ~~PCSK9i lipid stabilization period,~~ patients will return to the clinic for ***Month -2*** (Visit S3) ***followed by Month -1 (Visit S4) 30 days ± 3 days later. During these visits, Repatha will be administered, labs will be collected, and safety assessed.*** ~~The sole purpose of this~~ ***At*** visit ***S4,*** ~~is to determine entry~~ LDL-C ***will be checked a second time*** prior to randomization~~. The sole purpose of this visit is to determine entry LDL-C prior to randomization.~~ Patients with an LDL-C ≥70 mg/dL (via central or local lab) at this visit will qualify for randomization. Patients with LDL-C <70 mg/dL at Visit S***4*** will be screen failed and no further PCSK9i therapy will be administered. Day 1 should occur ~~immediately (ideally within 3 days)~~ ***30 days ±3 days*** after Visit S***4***, once LDL-C eligibility is established. On Day 1, qualified patients will be randomized 1:1 to bempedoic acid 180 mg/day (n = 26) or matching placebo (n = 26). Randomized patients will return for clinic visits at Month 1 (Visit T2) and Month 2 (Visit T3). Both study drug and PCSK9i doses will be administered on site during clinic visits after all procedures have been completed.

CHANGE 5 SUBJECT INCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis;
Section 7.1, Subject Inclusion Criteria

Original Text:

1. Provision of written informed consent must be obtained prior to any study-specific procedure.
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Month -2.5 (Visit S1)
3. Fasting, calculated LDL-C at screening (Month -1) ≥160 mg/dL and ≥70 mg/dL at Visit S3

Note: A single repeat of LDL-C may be completed. For those patients who have a repeat LDL-C, the average of the 2 values will be used to determine eligibility.

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

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

New Text:

1. Provision of written informed consent must be obtained prior to any study-specific procedure.
2. Age ≥18 years or legal age of majority depending on regional law, whichever is greater at Month -~~2~~*4*.5 (Visit S1)
3. Fasting, calculated LDL-C at screening (~~Month -1~~***Visit S2***) ≥160 mg/dL and ≥70 mg/dL at Visit ~~S3~~***S4***

   Note: A single repeat of LDL-C may be completed. For those patients who have a repeat LDL-C, the average of the 2 values will be used to determine eligibility.
4. Men and nonpregnant, nonlactating women. Women must be:
   a. Naturally postmenopausal defined as ≥1 year without menses and:
      – ≥55 years, **or**
      – <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L; **or**
   b. Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; **or**

c. Women of childbearing potential willing to use ~~1~~***2*** acceptable method***s*** of birth control including:

- oral, implanted, topical or injectable birth control medications
- placement of an intrauterine device with or without hormones
- barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
- vasectomized male partner who is the sole partner for this patient
- true abstinence (not including periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, or withdrawal)
- true abstinence***: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.)***~~(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.

CHANGE 6 SUBJECT EXCLUSION CRITERIA REVISIONS

Location:

Section 2, Synopsis;
Section 7.2, Subject Exclusion Criteria

Original Text:

1. Homozygous Familial Hypercholesterolemia (HoFH)
2. Total fasting TG ≥500 mg/dL (5.6 mmol/L) at Month -1 (Visit S2)

   Note: A single repeat of TG may be completed prior to initiation of the single-blind Run-in period. For those patients who have a repeat TG, the average of the 2 values will be used to determine eligibility.
3. Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Month -2.5 (Visit S1)

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the average of the 2 values be used to determine eligibility.
4. All patients with known cardiovascular disease (CVD) or peripheral arterial disease (PAD) or cerebrovascular disease (CD)

5. History of type 1 or type 2 diabetes or laboratory evidence of diabetes (fasting blood glucose [FBG] ≥126 mg/dL or glycosylated hemoglobin, Type A_{1C} (HbA_{1C}) >6.5%) without prior diagnosis of diabetes at Month -2.5 (Visit S1)
6. Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg at Month -2.5 (Visit S1)
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Month -2.5 (Visit S1)
8. Liver disease or dysfunction, including:
    a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Month -2.5 (Visit S1).
    b. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Month -2.5 (Visit S1).

    Note: If total bilirubin (TB) ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, the patient may be enrolled in the study.

    Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed. For those patients who have a repeat ALT and/or AST, the average of the 2 values will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but reflexive test for Hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption
10. History of hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Month -2.5 (Visit S1)
11. History of malignancy (except non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ)
12. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other meds for chronic pain that have been stable, without evidence of abuse prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
14. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood transfusion, or major surgery with or without blood loss within 30 days prior to randomization
15. Use of any experimental or investigational drugs within 30 days
16. Previous enrollment in an Esperion Phase 3 bempedoic acid (ETC-1002) clinical study

17. Use of a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to screening, such as: anacetrapib, dalcetrapib or evacetrapib
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Month -2.5 [Visit S1]),
    - Lomitapide or apheresis therapy (must be stopped at least 3 months prior to Month -2.5 [Visit S1]),
    - Red yeast rice containing products (must be stopped on or before Month -2.5 [Visit S1]),
    - Lipid regulating drugs or supplements (must be stopped on or before Month -2.5 [Visit S1])
19. Planned initiation or changes to the following drugs prior to Month -2.5:
    - Hormone replacement (6 weeks prior to Month -2.5)
    - Thyroid replacement (6 weeks prior to Month -2.5)
    - Obesity medication (3 months prior to Month -2.5)
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study
21. Patient is pregnant or breast feeding, or planning to become pregnant during treatment and/ or within 12 weeks after the end of treatment
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.

New Text:

1. Homozygous Familial Hypercholesterolemia (HoFH)
2. Total fasting TG ≥500 mg/dL (5.6 mmol/L) at Month ~~-1~~***3*** (Visit S2)

   Note: A single repeat of TG may be completed prior to initiation of the single-blind Run-in period. For those patients who have a repeat TG, the average of the 2 values will be used to determine eligibility.
3. Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m^2 at Month ~~-2~~***4***.5 (Visit S1)

   Note: A single repeat of eGFR may be completed prior to randomization. For those patients who have a repeat eGFR, the average of the 2 values be used to determine eligibility.
4. All patients with known cardiovascular disease (CVD) or peripheral arterial disease (PAD) or cerebrovascular disease (CD)

5. History of type 1 or type 2 diabetes or laboratory evidence of diabetes (fasting blood glucose [FBG] ≥126 mg/dL or glycosylated hemoglobin, Type A_{1C} (HbA_{1C}) >6.5%) without prior diagnosis of diabetes at Month ~~-2~~***4***.5 (Visit S1)
6. Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg at Month ~~-2~~***4***.5 (Visit S1)
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Month ~~-2~~***4***.5 (Visit S1)
8. Liver disease or dysfunction, including:
   a. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Month ~~-2~~***4***.5 (Visit S1).
   b. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-ABVivi) at Month ~~-2~~***4***.5 (Visit S1).

      Note: If total bilirubin (TB) ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, the patient may be enrolled in the study.

      Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed. For those patients who have a repeat ALT and/or AST, the average of the 2 values will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but reflexive test for Hepatitis C ribonucleic acid (RNA) is negative, patient can be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption
10. History of hematologic or coagulation disorders or a hemoglobin (Hgb) level <10 g/dL at Month ~~-2~~***4***.5 (Visit S1)
11. History of malignancy (except non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ)
12. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
13. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other meds for chronic pain that have been stable, without evidence of abuse prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
14. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood transfusion, or major surgery with or without blood loss within 30 days prior to randomization
15. Use of any experimental or investigational drugs within 30 days ***or 5 half-lives, whichever is longer***

16. Previous enrollment in an Esperion Phase 3 bempedoic acid (ETC-1002) clinical study
17. Use of a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to screening, such as: anacetrapib, dalcetrapib or evacetrapib
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must be stopped at least 6 months prior to Month ~~-2~~***4***.5 [Visit S1]),
    - Lomitapide or apheresis therapy (must be stopped at least 3 months prior to Month ~~-2~~***4***.5 [Visit S1]),
    - Red yeast rice containing products (must be stopped on or before Month ~~-2~~***4***.5 [Visit S1]),
    - Lipid regulating drugs or supplements (must be stopped on or before Month ~~-2~~***4***.5 [Visit S1])
19. Planned initiation or changes to the following drugs prior to Month ~~-2~~***4***.5:
    - Hormone replacement (6 weeks prior to Month ~~-2~~***4***.5)
    - Thyroid replacement (6 weeks prior to Month ~~-2~~***4***.5)
    - Obesity medication (3 months prior to Month ~~-2~~***4***.5)
20. A medical or situational (ie, geographical) finding that in the investigator's opinion may compromise the patient's safety or ability to complete the study
21. Patient is pregnant or breast feeding, or planning to become pregnant during treatment and/ or within ***30 days***~~12 weeks~~ after the end of treatment
22. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
23. ***Heterozygous familial hypercholesterolemia (HeFH)***
24. ***Concomitant use of a PCSK9 inhibitor (Praluent® [alirocumab] or Repatha® [evolocumab]) at (Visit S1) or prior use within the past 16 weeks of Visit S1***

CHANGE 7 PCSK9 INHIBITOR ADMINISTRATION CLARIFICATION

Location:

Section 2, Synopsis

Original Text:

Test product, dose, and mode of administration:

- Bempedoic acid 180-mg tablets/day
- Matching placebo tablets
- PCSK9i – Repatha 420 mg QM

All study drug (bempedoic acid or placebo) will be ingested once daily with or without food. On clinic days patients will come to the clinic in the fasted state and the PCSK9i and study drug will be administered after all study procedures have been conducted.

New Text:

Test product, dose, and mode of administration:

- Bempedoic acid 180-mg tablets/***once per*** day
- Matching placebo tablets***/once per day***
- PCSK9i – Repatha 420 mg ~~QM~~***injection once monthly***

All study drug (bempedoic acid or placebo) will be ingested once daily with or without food. On clinic days patients will come to the clinic in the fasted state and the PCSK9i and study drug will be administered after all study procedures have been conducted. ***PCSK9i injections must be administered consistently throughout the trial within 30 ± 3 days from the previous dose. Efficacy will vary if the doses are not consistently administered.***

CHANGE 8 REMOVAL OF ECG FROM SAFETY ASSESSMENTS

Location:

Section 2, Synopsis. This change also made as applicable in Sections 1.11, Safety Parameters; 13.7, Safety Endpoints; 14.1, Safety Monitoring; 17.3, Case Report Forms and Study Records; and Appendix 1 Schedule of Events (Subject Visit Schedule)

Original Text:

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

New Text:

Adverse events and serious adverse events (SAEs) will be collected and reported. Other safety assessments will include clinical safety laboratories (including hematology, blood chemistry, HbA_{1C}, fasting glucose, and urinalysis), physical examination (PE) findings, vital signs, ~~electrocardiogram (ECG) readings,~~ and weight.

CHANGE 9 STATISTICAL METHODS REVISIONS

Location:

Section 2, Synopsis
Section 13.2, Determination of Sample Size

Original Text:

Sample Size

The planned total sample size for this study is 52 with 26 patients in the bempedoic acid 180 mg group and in the placebo group. This sample size is expected to [redacted]

New Text:

Sample Size

The planned total sample size for this study is 52 with 26 patients in the bempedoic acid 180 mg group and ***26*** in the placebo group. This sample size is expected to [redacted]

CHANGE 10 REVISIONS TO STATISTICAL METHODS

Location:

Section 2, Synopsis
Section 13.5, Primary Endpoint

Original Text:

Primary Endpoint

The primary efficacy endpoint is the percent change from baseline to Month 2 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline LDL-C as a covariate. Baseline LDL-C is defined as the Day 1 value. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Patients who are missing their Month 2 LDL-C will have their Month 2 value imputed by last observation carried forward (LOCF). The least squares mean (LSM) and standard error (SE) for percent change estimate will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

New Text:

Primary Endpoint

The primary efficacy endpoint is the percent change from baseline to Month 2 in LDL-C. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline LDL-C as a covariate. ***The details of the ANCOVA***

model and options to correct for unequal variances will be described in the SAP. Baseline LDL-C is defined as the ***average of S4 and*** Day 1 values***, if only 1 value is available, then that single value will be used as baseline***. The ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Patients who are missing their Month 2 LDL-C will have their Month 2 value imputed by last observation carried forward (LOCF). The least squares mean (LSM) and standard error (SE) for percent change estimate will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

Location:

Section 13.6, Secondary and Exploratory Efficacy Endpoints

Original Text:

The secondary efficacy endpoints (percent change from baseline to Month 1 in LDL-C; change from baseline to Months 1 and 2 in LDL-C; percent change from baseline to Months 1 and 2 in ApoB, non-HDL-C,TC, hs-CRP [redacted] and [redacted], will be analyzed using the ANCOVA method similar to the primary endpoint. Baseline value for TC, non-HDL-C, [redacted] ApoB, and hs-CRP will be Day 1 value. Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Missing values will be imputed using LOCF, where applicable. For each parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p value.

New Text:

The secondary efficacy endpoints (percent change from baseline to Month 1 in LDL-C; change from baseline to Months 1 and 2 in LDL-C; percent change from baseline to Months 1 and 2 in ApoB, non-HDL-C,TC, hs-CRP [redacted] and [redacted], will be analyzed using the ANCOVA method similar to the primary endpoint. Baseline value for TC, non-HDL-C, [redacted] ***will be the average of S4 and Day 1 values;*** ApoB~~,~~ and hs-CRP will be **the** Day 1 value***, if only 1 value is available, the single value will be used as the baseline.*** Each ANCOVA will be performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. Missing values will be imputed using LOCF, where applicable. For each parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p value.

CHANGE 11 SAFETY ENDOINT REVISIONS

Location:

Section 2, Synopsis;
Section 13.7, Safety Endpoints

Original Text:

Musculoskeletal Safety

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

Diabetes/Hyperglycemia

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

Renal Safety

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

New Text:

Musculoskeletal Safety

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

Diabetes/Hyperglycemia

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

Renal Safety

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

CHANGE 12 INVESTIGATIONAL PLAN REVISIONS

Location:

Section 6.3, Study Duration and Period
Section 6.4, End of Study

Original Text:

6.3 Study Duration and Period

The duration of treatment will be 18 weeks (2.5-month screening period, a 1-month lipid-stabilization period, and 2-month treatment period).

6.4 End of Study

The study will end when the last randomized patient completes the Month 2 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately 8 months.

New Text:

6.3 Study Duration and Period

The duration of treatment will be ***26***~~18~~ weeks (***1***~~2~~.5-month screening period, a ***3***~~1~~-month lipid-stabilization period, and 2-month treatment period).

6.4 End of Study

The study will end when the last randomized patient completes the Month 2 visit. The estimated overall duration of the study (first patient first visit [FPFV] to last patient last visit [LPLV]) is approximately ***10.5***~~8~~ months.

Location:

Section 6.6.1, Screening and 1 Month PCSK9i Run-in Period

Original Text:

Screening will occur approximately 10 weeks prior to Day 1 (Visit T1). Eligible patients will return to the clinical site at Month -1 (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate PCSK9i background therapy (Repatha 420 mg QM). No other background lipid-modifying therapy except study provided PCSK9i will be permitted during the trial.

New Text:

Screening will occur approximately ***18***~~10~~ weeks prior to Day 1 (Visit T1). Eligible patients will return to the clinical site at Month ~~-1~~***3*** (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate ***study-provided*** PCSK9i background therapy (Repatha 420 mg QM). No other background lipid-modifying therapy except study provided PCSK9i will be permitted during the trial.

Location:

Section 6.6.2, Randomization and Treatment Period;

Original Text:

Patients who satisfy all entry criteria, complete the 2.5-month screening period and 1-month (at least 30 days) PCSK9i run-in period and have an LDL-C ≥70 mg/dL at S3 will be randomized. Randomization numbers will be assigned via IWRS on Day 1 (Visit T1). Patients will be randomized in a ratio of 1:1 to receive 1 of the following 2 treatments in a double-blind fashion:

- Bempedoic acid 180-mg tablet
- Matching placebo tablet

New Text:

Patients who satisfy all entry criteria, complete the ***1.5***~~2.5~~-month screening period and ***3***~~1~~-month ~~(at least 30 days)~~ PCSK9i run-in period and have an LDL-C ≥70 mg/dL at S***4***~~3~~ will be randomized. Randomization numbers will be assigned via IWRS on Day 1 (Visit T1). Patients

will be randomized in a ratio of 1:1 to receive 1 of the following 2 treatments in a double-blind fashion ***in addition to monthly PCSK9i background therapy***:

- Bempedoic acid 180-mg tablet
- Matching placebo tablet

CHANGE 13 ADMINISTRATION OF MEDICINAL PRODUCT REVISION

Location:

Section 9.2, Administration of Investigational Medicinal Product

Original Text:

PCSK9i will be administered on site at Visits S2, T1, and T2. Doses will be stored and administered as required in prescribing information

New Text:

PCSK9i will be administered on site at Visits S2, ***S3, S4,*** T1, and T2. Doses will be stored and administered as required in prescribing information

CHANGE 14 STUDY PROCEDURES REVISIONS

Location:

Section 10.2, Procedures and Schedule of Assessments

Original Text:

10.2.1 Screening Month -2.5 (Visit S1)

The screening period will begin with a screening visit that will occur approximately 10 weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history
- Concomitant and prohibited medication review
- Height (cm), weight (kg), body mass index (BMI)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ApoB and hs-CRP
  - HbA_{1C}

  - PCSK9i
  - TSH
  - FSH (in appropriate female patients)
  - Serum pregnancy test (on appropriate female patients)
- Serology (including HBsAg, Hepatitis C virus [HCV])
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

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

10.2.2 PCSK9i Run-in Month -1 (Visit S2)

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

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

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination (PE)
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
- ApoB and hs-CRP
- PCSK9i
- First PCSK9i injection. Verification of lipid entry criteria (LDL-C value of >160 mg/dL and triglycerides <500 mg/dL) must be obtained before starting PCSK9i
- Schedule next visit **(S3 has to be at least 30 days from first dose of PCSK9i)**

Note: Local labs can be used to assess LDL-C and TGs for entry. If using a central lab or a local lab with a delay in obtaining results, an optional visit to administer PCSK9i may be scheduled. **Patients need to be on Repatha 420 mg for at least 30 days during the lipid stabilization period before conducting Visit S3.**

10.2.3 Screening/Prerandomization (Visit S3)

One month (30 days) from S2, patients will have their LDL-C evaluation (local or central) prior to randomization.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Obtain fasting LDL-C
- Schedule next visit Day 1 **(Day 1 should occur immediately [ideally within 3 days] after S3, once LDL-C eligibility [≥70 mg/dL] is established)**

Note: Central lab LDL-C results may take up to 3 days to obtain, so please plan accordingly if using the central lab**.**

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

Prior to scheduling Visit T1, review S1, S2, and S3clinical results to evaluate whether the patient continues to meet eligibility criteria.

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

If the patient has met all inclusion criteria, none of the exclusion criteria, and has been on Repatha 420 mg **for at least 30 days**, the patient may be randomized into the double-blind treatment period. Patients who fail to meet any entry criterion prior to randomization are considered to be screen failures, will not be randomized into a treatment group, and are not required to return for additional visits. Patients are considered randomized once all eligibility criteria are confirmed and a randomization number is obtained by the IWRS on the day of first dose.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis

    Note: Urine pregnancy test (for females of childbearing potential)
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ApoB and hs-CRP
  - HbA_{1C}
- Predose PCSK9i and PK

- Review inclusion/exclusion criteria to establish patient eligibility. **Patient must have an LDL-C ≥70 mg/dL on S3 before they can be randomized on Day 1.**

- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions (two 35-day supply bottles)
  - **Subject should be randomized and receive IMP within 3 days of S3, as soon as the final LDL-C entry criterion is met**
- PCSK9i injection and IMP must be given at the end of procedures
- Schedule next visit

10.2.5 Treatment Month 1 (Visit T2 ±3 days)

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

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

Patients will undergo the following assessments and procedures at Month 1 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
- Predose PCSK9 and PK. Should be taken ideally within 4 hours of the patient's normal time of dosing
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- Re-dispense IMP container from Visit T1 to patient for continued dosing and provide dosing instruction
- PCSK9i injection and IMP must be given at the end of procedures
- Schedule next visit

10.2.6 Treatment Month 2 (Visit T3 ±3 days)

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

New Text:

10.2.1. Screening Month ~~-2.5~~ *−4.5* (Visit S1)

The screening period will begin with a screening visit that will occur approximately ~~10~~***18*** weeks prior to randomization. Visit S1 will allow the Investigator to assess the patient's preliminary eligibility. After the patient provides written informed consent (see Section 10.1), the patient will undergo the following assessments and procedures at Visit S1:

- Demographics
- Clinically relevant medical history
- Concomitant and prohibited medication review
- Height (cm), weight (kg), body mass index (BMI)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ~~ApoB and hs-CRP~~
  - HbA_{1C}
  - ~~PCSK9i~~
  - TSH
  - FSH (in appropriate female patients)
  - Serum pregnancy test (on appropriate female patients)
- Serology (including HBsAg, Hepatitis C virus [HCV])
- Review of all inclusion/exclusion criteria that can be assessed at this time
- Conduct diet and exercise counseling
- Contact IWRS to register the patient

Patients who meet all enrollment criteria that can be assessed following review of the S***1*** central clinical laboratory results (available several days after Visit S1) will be instructed to washout of all lipid-regulating drugs and 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).

10.2.2. PCSK9i Run-in Month ~~-1~~*3* (Visit S2)

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

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

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Physical examination (PE)
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
- ApoB and hs-CRP
- ~~PCSK9i~~
- First PCSK9i ***monthly*** injection. Verification of lipid entry criteria (LDL-C value of >160 mg/dL and triglycerides <500 mg/dL) must be obtained before starting PCSK9i
- Schedule next visit **(S3 has to be at least 30 days ±*3 days* from *the* first dose of PCSK9i)**
  - ***PCSK9i injections must be administered consistently throughout the trial within 30 ± 3 days from the previous dose. Efficacy will vary if the doses are not consistently administered.***

  Note: Local labs can be used to assess LDL-C and TGs for entry. All other labs must be ***run via the central lab.*** If using a central lab or a local lab with a delay in obtaining results, an optional visit to administer PCSK9i may be scheduled. **Patients need to be on Repatha 420 mg for at least 30 days ±*3 days* ~~during the lipid stabilization period~~ before conducting Visit S3.**

10.2.3. PCSK9i Run-in Month -2 ~~Screening/Prerandomization~~ (Visit S3)

~~One month (30 days) from S2, patients will have their LDL-C evaluation (local or central) prior to randomization.~~***Prior to scheduling Visit S3, review the screening clinical results to evaluate whether the patient continues to meet eligibility criteria.***

- ***If the patient meets eligibility criteria, then schedule the Visit S3 and proceed with the Visit S3 procedures***

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- ~~Obtain~~ ***Vital signs***
- ***Basic*** fasting ***lipids (TC, calculated*** LDL-C***, [redacted], non-HDL C, [redacted], and [redacted])***

- ***PCSK9i monthly injection must be given at the end of procedures***

~~Note: Central lab LDL-C results may take up to 3 days to obtain, so please plan accordingly if using the central lab.~~

10.2.4 PCSK9i Run-in Month -1 (Visit S4)

One month (30 ± 3 days) from S3, patients will have their LDL-C evaluated a second time via **central lab only** prior to randomization on Day 1.

The patient will undergo the following assessments and procedures at (Visit S4)

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Vital signs
- Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - Schedule next visit Day 1 **(<u>Day 1 should occur ~~immediately~~ 30 ±3 days after S4, once LDL-C eligibility [≥70 mg/dL] is established</u>)**
- ***PCSK9i monthly injection must be given at the end of procedures***

~~10.2.4.~~*10.2.5.* Treatment Week 0 (Visit T1; Day 1)

Prior to scheduling Visit T1, review S1, S2, ***S3***, and S~~3~~***4*** clinical results to evaluate whether the patient continues to meet eligibility criteria.

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

If the patient has met all inclusion criteria, none of the exclusion criteria, and has been on Repatha 420 mg ***for 30 ±3 days during each month of the PCSK9i run-in period***, the patient may be randomized into the double-blind treatment period. Patients who fail to meet any entry criterion prior to randomization are considered to be screen failures, will not be randomized into a treatment group, and are not required to return for additional visits. Patients are considered randomized once all eligibility criteria are confirmed and a randomization number is obtained by the IWRS on the day of first dose.

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

- Concomitant and prohibited medication review (ongoing)
- Assess AEs (starting from signing of the informed consent document)
- Weight
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Note: Urine pregnancy test (for females of childbearing potential)
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])

  - ApoB and hs-CRP
  - HbA_{1C}
- Predose ~~PCSK9i and~~ PK
- Review inclusion/exclusion criteria to establish patient eligibility. **Patient must have an LDL-C ≥70 mg/dL ~~on S3~~ *at S4* before they can be randomized on Day 1.**
- Conduct diet and exercise counseling
- IWRS contact to obtain the patient randomization number and MED ID number for double-blind study drug
- Dispense IMP and provide dosing instructions (~~two~~ 35-day supply bottles)
  - **Subject should be randomized and receive IMP within *30* ± 3 days of *S4*~~S3~~, as soon as the final LDL-C entry criterion is met**
- PCSK9i injection and IMP must be given at the end of procedures
- Schedule next visit

~~10.2.5~~*10.2.6.* Treatment Month 1 (Visit T2 ±3 days)

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

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

Patients will undergo the following assessments and procedures at Month 1 (Visit T2):

- Concomitant and prohibited medication review (ongoing)
- Assess AEs since last visit (ongoing)
- Vital signs
- Clinical laboratory evaluations:
  - Hematology, blood chemistry, and urinalysis
  - Basic fasting lipids (TC, calculated LDL-C, [redacted], non-HDL-C, [redacted], and [redacted])
  - ***ApoB and hs-CRP***
- Predose ~~PCSK9 and~~ PK. Should be taken ideally within 4 hours of the patient's normal time of dosing
- Conduct diet and exercise counseling
- Return of IMP; assessment and recording of IMP compliance
- ~~Re-dispense~~ ***Dispense*** IMP ~~container from Visit T1 to patient for continued dosing~~ and provide dosing instruction***s (35-day supply bottles)***
- PCSK9i injection and IMP must be given at the end of procedures
- Schedule next visit

~~10.2.6~~*10.2.7* Treatment Month 2 (Visit T3 ±3 days)*/EOS*

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

CHANGE15 ASSESSMENT OF SAFETY REVISION

Location:

Section 11.1, Safety Parameters

Original Text:

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

New Text:

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

CHANGE 16 REPORTING ADVERSE EVENTS REVISIONS

Location:

Section 12.1.3, Reporting for Adverse Events

Original Text:

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

New Text:

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs***, as described below***. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. 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.

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***

CHANGE 17 ELEVATED CK MONITORING REVISION

Location:

Section 11.1.5.4.3, Monitoring and Management of Elevated Creatinine Kinase

Original Text:

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

Repeat CK assessment will include query for related symptoms.

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

New Text:

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

Repeat CK assessment will include query for related symptoms.

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

CHANGE 18 ADVERSE EVENT MONITORING REVISION

Location:

Section 12.1.3, Reporting for Adverse Events

Original Text:

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

New Text:

Clinically significant abnormal laboratory or other examination findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs***, as described below***. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. 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.

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***

Location:

Section 12.6.1, Monitoring and Follow-up of Adverse Events

Original Text:

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 12.2.2).

New Text:

Patients with AEs related to IMP that are ongoing at study discontinuation or completion must be followed until resolution***, until deemed stable/chronic,*** or for 30 days after study completion, whichever comes first, with the exception of patients reporting SAEs (see Section 12.2.2).

CHANGE 19 SERIOUS ADVERSE EVENT DEFINITION ADDITION

Location:

Section 12.2.1., Definition of Serious Adverse Event

Original Text:

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.

New Text:

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.

Events or Outcomes Not Qualifying as Serious Adverse Events

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

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

Location:

Section 12.2.2, Reporting Serious Adverse Events

Original Text:

To report the SAE, the SAE form in 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.

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.

New text:

To report the SAE, the SAE ~~form in EDC should be completed~~***information should be entered on to the AE eCRF in the EDC database*** within 24 hours of becoming aware of the event. If you have questions, please call the designated Safety contact for assistance.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE ~~form~~ ***information on the AE eCRF*** and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to designated Safety contact.

Location:

Section 12.2.3, Reporting of Patient Death

Original Text:

The death of any patient during the study or within 30 days after the last dose of bempedoic acid must be reported as an SAE.

New Text:

The death of any patient during the study or within 30 days after the last dose of ~~bempedoic acid~~ ***study treatment*** must be reported as an SAE.

CHANGE 20 PREGNANCY REPORTING REVISION

Location:

Section 12.2.4, Reports of Pregnancy and Lactation

Original Text:

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.

New Text:

Although not considered an SAE (unless an event occurs with a serious outcome), ***any event of*** pregnancy will be collected by the designated Safety contact. If a female patient should become pregnant during the course of the study ***or within 30 days after last dose of study treatment***, the Principal Investigator or designee must contact the designated Safety contact within 24 hours of knowledge of the pregnancy. In addition, a ***paper*** Pregnancy ***R***~~r~~eport ***F***~~f~~orm 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 ***paper*** Pregnancy Outcome ***R*~~r~~eport ***F*~~f~~orm must be completed and submitted to the Safety contact. Patients who ***are breastfeeding are excluded from this*** ~~lactate during the~~ study ~~may be required to~~ ***and should*** discontinue study medication.

CHANGE 21 STATISTIC REVISION

Location:

Section 13.9, PCSK91

Original Text:

13.9 PCSK91

PCSK9 concentrations will be collected and summarized from patients at S1, S2, T1, T2, and T3.

New Text:

~~**13.9 PCSK91**~~

~~PCSK9 concentrations will be collected and summarized from patients at S1, S2, T1, T2, and T3.~~

CHANGE 22 CASE REPORT FORMS AND STUDY RECORDS REVISION

Location:

Section 17.3, Case Report Forms and Study Recrods

Original Text:

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

New Text:

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

CHANGE 23 SCHEDULE OF EVENTS REVISION

Location:

Appendix 1, Schedule of Events

Original Text:

Schedule of Events						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/EOS)[3]**
Week	**Month -2.5**	**Month** -1	**Pre-randomization**	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day -75**	**Day -30±3**	**30 days post-S2**	**Day 1***	**Day 31±3**	**Day 61±3**
Informed Consent	X					
Enrollment Criteria	X	X				
Demographics	X					
Medical History	X					
Concomitant Medications	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X
Physical Exam		X				X
Weight[4]	X			X		X
Height	X					
Vital Signs[6]	X	X		X	X	X
Serology[7]	X					
Serum Pregnancy/FSH[8]	X					
Urine pregnancy test for women of childbearing potential only				X		
TSH	X					
Clinical Safety Labs[9]	X			X	X	X
Basic Fasting Lipids[10]	X	X**	X***	X	X	X
ApoB and hs-CRP		X		X		X
HbA_{1C}	X			X		X
PCSK9	X	X		X	X	X
PK – predose trough				X	X	X
Diet and exercise counseling[11]	X	X		X	X	X
Establish Patient Eligibility				X		
Randomization				X		
IWRS Contact[12]	X			X	X	X
PCSK9i administered at site		X		X	X	
Double-blind Drug Dispensing				X	X	

Schedule of Events						
Visit	**S1[1,2]**	**S2**	**S3**	**T1**	**T2**	**T3/EOS)[3]**
Week	**Month -2.5**	**Month** -1	**Pre-randomization**	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day -75**	**Day -30±3**	**30 days post-S2**	**Day 1***	**Day 31±3**	**Day 61±3**
IMP Return/Compliance					X	X
PCSK9i Return/Accountability		X		X	X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T4 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

[1] An optional basic fasting lipid MAY be completed prior to S2, but must occur just prior to the next witnessed PCSK9i dose if patient fails to meet lipid entry criterion at Visit S1. If this optional basic fasting lipid is completed, the average of the 2 lipid values will be used to determine eligibility.

[2] A recheck of blood pressure may be completed prior to T1 if the patient's diastolic blood pressure (DBP) and/or systolic blood pressure (SBP) meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. Repeat labs may be completed prior to T1 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

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

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

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

[7] Serology for HBsAg, HCV-ABVivi

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

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.

[10] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), [redacted] non-HDL-C,), and [redacted]).

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

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

* Patients must be on PCSK9 for at least 30 days before initiating Day 1. Day 1 should occur immediately (ideally within 3 days) after S3, once LDL-C eligibility is established

** LDL-C must be ≥160 mg/dL and TG <500 mg/dL before initiating PCSK9i. A local lab may be used to assess LDL-C and TG.

*** LDL-C must be ≥70 mg/dL to qualify for randomization. A local lab may be used to assess entry LDL-C.

New Text:

	Schedule of Events						
Visit	**S1**[1,2]	**S2**	***S3***	**S3**	**T1**	**T2**	**T3/EOS)**[3]
~~Week~~ *Month*	**Month ~~-2~~*4*.5**	**Month ~~-1~~*3***	**~~Pre-randomization~~ *Month -2***	***Month -1***	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day ~~-7~~*13*5**	**Day~~-3~~9*0* ±3**	**Day ~~1*~~-*60* ±*3***	**Day ~~31~~-*30* ±3**	**Day ~~61±3~~1***	**Day31 ±3**	**Day61 ±3**
Informed Consent	X						
Enrollment Criteria	X	X	***X***	***X***			
Demographics	X						
Medical History	X						
Concomitant Medications	X	X	***X***	X	X	X	**X**
Adverse Event Recording		X	***X***	X	X	X	X
Physical Exam		X				~~X~~	X
Weight[4]	X				X	~~X~~	X
Height	X						
Vital Signs[6]	X	X	***X***	X	X	X	X
Serology[7]	X						
Serum Pregnancy/FSH[8]	X						
Urine pregnancy test for women of childbearing potential only					X		
TSH	X						
Clinical Safety Labs[9]	X				X	X	X
Basic Fasting Lipids[10]	X	X**	***X******	X***	X	X	X
ApoB and hs-CRP		X			X	***X***	X

	Schedule of Events						
Visit	**S1**[1,2]	**S2**	***S3***	**S3**	**T1**	**T2**	**T3/EOS)**[3]
~~Week~~ *Month*	**Month ~~-2~~*4*.5**	**Month ~~-1~~*3***	**~~Pre-randomization~~ *Month -2***	***Month -1***	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day ~~-7~~*13*5**	**Day~~-3~~*9*0 ±3**	**Day ~~1*-~~*60* ±*3***	**Day ~~31-~~*30* ±3**	**Day ~~61±3~~1***	**Day31 ±3**	**Day61 ±3**
HbA_{1C}	X				X		X
~~PCSK9~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X~~	~~X~~
PK – predose trough					X	X	X
Diet and exercise counseling[11]	X	X			X	X	X
Establish Patient Eligibility					X		
Randomization					X		
IWRS Contact[12]	X				X	X	X
PCSK9i administered at site		X	***X***	X	X	X	
Double-blind Drug Dispensing					X	X	
IMP Return/Compliance						X	X
PCSK9i Return/Accountability		X	***X***	X	X	***X***	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), ***and*** vital signs~~, and electrocardiograms (ECGs)~~. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit T4 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

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[3] All procedures will be completed for all patients at either ***T3/***EOS if completing the study or early withdrawal.

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

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

* Patients must be on PCSK9 for ~~at least~~ 30 ± ***3*** days ***during each month of the PCSK9 run-in period*** before initiating Day 1. ~~Day 1 should occur immediately (ideally within 3 days) after S3, once LDL-C eligibility is established~~

** LDL-C must be ≥160 mg/dL and TG <500 mg/dL before initiating PCSK9i. A local lab may be used to assess LDL-C and TG ***for eligibility prior to initiating Repatha, but a central lab must also be conducted at this visit.***

*** LDL-C must be ≥70 mg/dL to qualify for randomization. ~~A local~~ ***Only a central*** lab may be used to assess entry LDL-C.

CHANGE 24 SPONSOR'S SIGNATURE PAGE REVISIONS

Location:

Appendix 2, Sponsor's Signature

Original Text:

Study Title:	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy
Study Number:	1002-039
Final Date:	22 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: _____ Date: _____

[redacted]

New Text:

Study Title:	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when added to PCSK9-Inhibitor Therapy
Study Number:	1002-039
Final Date:	***05 March 2017***~~22 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: _____ Date: _____

[redacted]